THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—36TH YEAR. SYDNEY, SATURDAY, JULY 2, 1949. No. 1.

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THE MICROBIOLOGICAL ASSAY OF VITAMINS.

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MICROBIOLOGICAL METHODS for the quantitative assay of certain vitamins and amino acids are now widely used in America, and, to a less extent, in England. All members of the vitamin *B* complex and all the amino acids can be measured in this way, and the same methods can also be extended to certain other nutrients such as potassium. This type of assay has the advantage of requiring only simple apparatus, and it can readily be used in small hospital laboratories, therefore, where the workers usually possess a knowledge of routine bacteriological procedures. Nevertheless microbiological assays are still not used as much as is justified and this article is written in the hope of making them more widely known. It is proposed to give a general account of the methods and then to describe in detail the estimation of riboflavin, nicotinic acid (niacin) and folic acid. The first of these methods deserves recognition as the original example of the use of lactobacilli for microbiological assays; the second is one of the most accurate of the group; and the third is being actively developed at the present time.

General Scope of Microbiological Assays.

The microorganisms used in these assays are mostly bacteria, yeasts or moulds. Now these organisms belong to the plant kingdom, and, by conventional definition, the term "vitamin" is restricted to certain nutrients essential for animals. The problem arises, then, of the relationship between the so-called growth factors required by microorganisms and the vitamins required by animals.

The relationship is, in many cases, a simple one: the same chemical substance can function both as a growth factor and as a vitamin. Riboflavin, for example, is necessary for certain metabolic processes in animals; it is equally necessary for the growth of lactobacilli. Similarly, niacin protects us from pellagra; it also enables the staphylococcus to live out its life in the normal way. There is a certain fundamental similarity in the metabolism of cells, even when the cells are obtained from such widely differing sources as bacteria, on the one hand, and higher animals, on the other. Nevertheless, the idea of the identity of certain growth factors and vitamins was, until recently, a revolutionary one. Perhaps we accept it readily enough today, but as late as 1936 Knight wrote in his classic monograph on bacterial nutrition: "At present it has not been shown that any pure animal vitamin is required as an essential nutrient by any bacteria".[(3)] It should be noted that Knight was referring specifically to bacteria. In the case of the fungus, *Phycomyces blakesleeanus*, Schopper had demonstrated in 1935 that vitamin B_1 was an essential growth factor. This was the earliest instance of a vitamin being shown to be indispensable for the growth of a microorganism, and it is interesting to note that attempts were soon made to use this organism in the microbiological assay of vitamin B_1.

We may speculate as to what might have happened if the identity of certain growth factors and vitamins had been appreciated earlier. The work of isolating members of the vitamin *B* complex would have developed more quickly, because slow macrobiological tests could have been replaced by rapid microbiological methods. Had workers in animal nutrition accepted a hint when nicotinic acid was shown to be a growth factor for staphylococci, then the role of nicotinic acid in preventing pellagra might have been found out much earlier. The work on the more recently discovered para-aminobenzoic acid, biotin, pantothenic acid, pyridoxal, pyridoxamine, inositol and folic acid has been speeded up by the use of microbiological methods. All of these nutrients, except folic acid, were first

[1] A report of work commenced at the Institute of Anatomy, Commonwealth Department of Health, Canberra.

investigated as growth factors and were tried as vitamins only after much of the fundamental work had been carried out with the aid of microorganisms. In future, any substance that may be found active as a growth factor will certainly be tested for possible activity as a vitamin. It is interesting to see that this method of approach has already proved fruitful to the Americans in their work on the recently isolated anti-pernicious anæmia factor, vitamin B_{12}; but it should be noted that the English workers isolated the same substance at about the same time without the use of microbiological assays. The latter workers depended on clinical trials to assay their products; but they probably would not have proceeded so far if their work had not been incidental to the important practical problem of obtaining more and more refined liver extract for use in the treatment of pernicious anæmia.

Principles of Microbiological Assays.

Before a microbiological method for the assay of any vitamin can be developed, three conditions must be satisfied:

1. It is necessary to have a microorganism which requires, as a growth factor, the vitamin under consideration. Thus microbiological assays are not available for vitamins *A* and *D*, because these vitamins are not known to be required by any microorganism. On the whole it would seem unlikely that a microbiological assay could ever be developed for these two vitamins. The position in regard to vitamins *C*, *K* and *E* is more uncertain; though at the present time these substances are not assayed microbiologically.

2. It is necessary to know sufficient about the nutrition of the organism to be able to make a basal medium which contains all the essential nutrients, apart from the vitamin that is being assayed. It may be possible to make this medium from substances of known chemical composition; but it is cheaper, and in many cases just as satisfactory, to use a type of medium that has been given the name of "semi-synthetic". This is a medium in which specially treated extracts of substances such as yeast, liver or peptone provide rich natural sources of some of the expensive nutrients required. The necessity of providing a suitable basal medium in microbiological assays links this work with studies on bacterial nutrition.

3. Finally, when varying amounts of the vitamin which it is desired to assay are added to the basal medium, the test organism must give responses which, within certain limits at any rate, are related to the amount of vitamin added. There are many lactobacilli which require riboflavin and for which an appropriate basal medium can readily be made, but which are unsuitable for the assay of riboflavin, because the response of the organism is not a function of the amount of vitamin present.

Nutritional Requirements of Lactic Acid Bacteria.

It was in the course of a study on the nutritional requirements of lactic acid bacteria that Snell and his colleagues developed the method for the assay of riboflavin. Microbiological assays can be considered as one practical application of fundamental work on the nutrition of microorganisms.

Lactobacilli, unlike many soil bacteria, have lost the power of synthesizing certain amino acids and vitamins, and have to rely upon external sources of supply. They require, for their normal metabolism and growth, a source of energy, such as glucose, together with amino acids, mineral salts and certain vitamins. It is believed that some of these organisms require certain amino acids in the form of peptides such as strepogenin. The requirements for vitamins, amino acids and minerals are indicated in Table I. These lists have been taken from those given by Snell[6][7] and by MacLeod and Snell.[3]

In Table I the positive denotes that in the absence of the nutrient, the organism indicated does not grow. The negative sign denotes that the nutrient is not required for growth. It frequently happens, however, that one or other of these non-essential substances is stimulatory to growth.

A point of practical importance is the question of whether the nutritional requirements vary from time to time. They do to some extent. For example, we have had experience of *Lactobacillus casei* varying in its requirement for riboflavin. At one time the yeast used in our yeast-water-glucose-agar tubes was deficient in this vitamin. The organisms adapted themselves to the low level of riboflavin and then gave maximal acid production in media containing very small amounts of the vitamin. This is a warning to keep stock cultures on enriched media; but in practice, if this precaution is observed, it is not found that adaptation of the organism to changes in environment is an important source of error in assays.

TABLE I.

Requirements of Various Species of Lactic Acid Bacteria for Vitamins, Amino Acids and Minerals.

Substance.	*Lactobacillus casei.*	*Lactobacillus arabinosus.*	*Streptococcus faecalis* Rogers.
Riboflavin	+	−	−
Pantothenic acid	+	+	+
Nicotinic acid	+	+	+
Biotin	+	+	+
Pyridoxin	+	−	+
Thiamine	−	−	−
Folic acid	+	−	+
Aspartic acid	+	−	+
Glutamic acid	+	+	+
Arginine	+	−	+
Histidine	−	−	−
Lysine	−	−	+
Alanine	−	−	+
Cystine	+	+	−
Glycine	−	−	+
Isoleucine	−	+	+
Leucine	+	+	+
Methionine	−	−	−
Phenylalanine	+	−	−
Proline	−	−	−
Serine	+	−	+
Threonine	−	−	+
Tryptophan	+	+	+
Tyrosine	+	−	−
Valine	+	+	−
Manganese	+	+	−
Magnesium	−	−	−
Potassium	+	+	+
Iron	−	−	−
Phosphate	+	+	−

General Outline of Method of Assay.

The general procedure is to compare the response of the microorganisms to known amounts of the substance being assayed, with their response to known amounts of the vitamin under consideration. For instance, when the riboflavin content of cow's milk is being measured, a comparison is made between the response of the organisms to various small quantities of milk and their response to known amounts of riboflavin; and if the response to, say, 0·1 microgramme of riboflavin is the same as that obtained with 0·05 millilitre of milk, then one concludes that 0·05 millilitre of milk contains 0·1 microgramme of riboflavin. In doing this, one assumes that, under the conditions of the test, riboflavin is the only constituent of the milk that affects the growth of the organism. This assumption is examined critically later on.

As the response of the organism to known amounts of riboflavin varies somewhat from day to day, according to the conditions of the test, it is necessary to determine the standard curve each time a test is carried out. The procedure, as used in the earliest type of microbiological assay, is illustrated by Figure I and the accompanying legend.

The points representing the acid production corresponding to various levels of riboflavin are plotted, and a freehand curve is drawn through them. The amount of riboflavin corresponding to the acid produced in the tubes containing wheat extract is then read directly from the graph. For example, the tubes containing the extract from 1/20 gramme of wheat gave an average titration figure of 3·41 millilitres, which is equivalent to 0·057 microgramme of riboflavin. In a similar way the extract from

1/15 gramme of wheat is estimated to contain 0·078 microgramme of riboflavin; and that from 1/12 gramme to contain 0·096 microgramme. Thus the three results for the riboflavin content of wheat are 1·14, 1·17 and 1·15 microgramme per gramme.

It is not usual for the lower part of the graph to be concave upwards as in Figure I.

Description of a Typical Assay.

A typical test is as follows. Five millilitres of basal medium are added to each of two series of test tubes which are 16 to 22 millimetres in width and 150 millimetres in length. The vitamin to be assayed is added in graded amounts to one series, whilst graded amounts of the test substance are added to the other. The volume of the contents of each tube is then adjusted, where necessary, to approximately 10 millilitres with glass-distilled water.

General Technical Problems.

Sterilization.

The sterilization carried out is usually only nominal, and is not successful if bacterial spores are present. A thorough sterilization cannot be carried out because it leads to caramelization of the medium, and resulting difficulty in measuring the growth of the organisms. Occasionally a whole assay may be spoilt, owing to the presence of foreign bacterial growth. It is true that the autoclaving is not as thorough as one would desire, but carelessness about sterility is to be strongly deprecated. We wish to emphasize that the estimation is essentially a bacteriological procedure.

There is a secondary function of autoclaving. Snell points out that many lactobacilli will not grow in unautoclaved medium; so that in these cases some chemical reaction most likely occurs in the medium during autoclaving.[9]

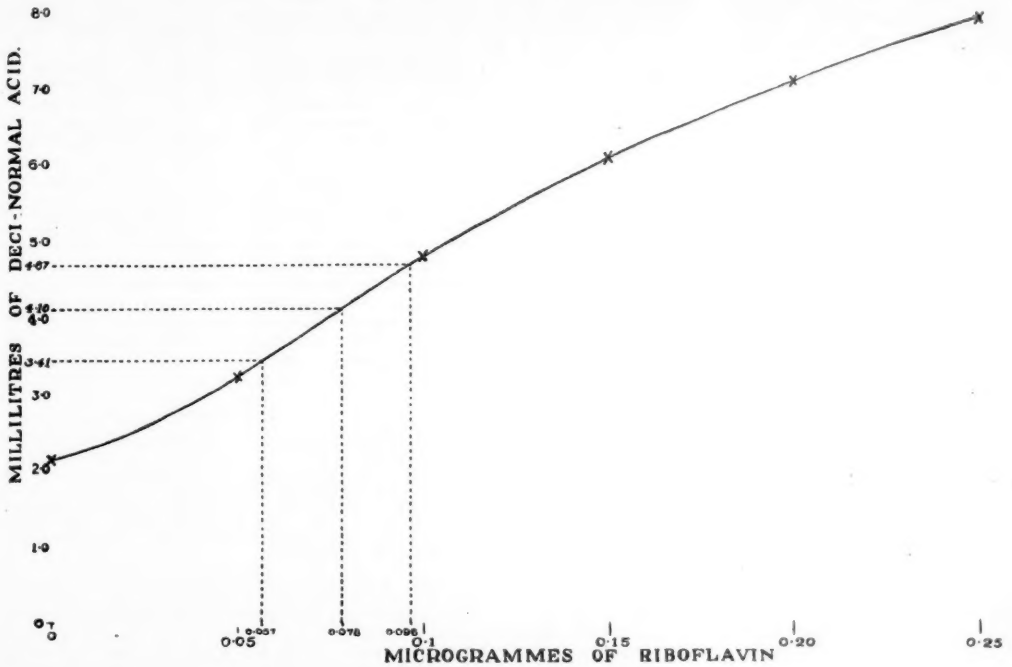

FIGURE I.

Since a certain amount of growth is always obtained upon the vitamin-free medium, "blank" estimations should be included. Each level of the standard vitamin solution and of the test substance should be set up in duplicate at least, and each assay of the test substance should be carried out at some three different levels of concentration.

The tubes are plugged with cotton wool and are sterilized in a autoclave. They are then allowed to cool, and are inoculated. According to some workers, it is advisable to delay the inoculation until the following day, for this may result in lower "blank" readings. This effect is perhaps due to chemical reactions within the medium.

After inoculation the tubes are incubated at the required temperature for a number of hours. The incubator must not show a temperature gradient, for otherwise the maximum agreement between replicates will not be obtained. When the period of incubation is over, the tubes are steamed for 10 to 20 minutes in the autoclave, in order to kill the bacteria. The growth is then measured.

It will be seen that the method is relatively more time-saving when several analyses are carried out in the same batch. The processes of sterilization and of preparing basal medium and inoculum are as simple on a large batch as on a small.

The Inoculum.

The final amount of growth is dependent upon the concentration of the vitamin that is being assayed, and is not materially influenced by the size of the inoculum, if the inoculum is well washed.[10] In most assays a light inoculum is used.

Measurement of Growth.

Various methods for the measurement of growth are available. The technique for the counting of individual bacteria is time-consuming, and is relatively inaccurate. In general it would be quite unsuitable for the purpose of microbiological assay. Three other methods are, however, available.

(i) Measurement of some substance produced during the growth of the bacteria in an amount proportional to the growth. The lactobacilli, for instance, produce lactic acid, and this can be measured directly by titration. The amount produced ranges from about two to ten millilitres of tenth normal acid per tube, and this is titrated against approximately tenth normal or twentieth normal sodium hydroxide; a suitable indicator is used, such as one drop of a 0·4% solution of bromthymol blue. In the folic acid assay a more convienent indicator is a 0·4% solution of

thymol blue (three parts) screened with 0·4% cresol red (one part); three drops of the solution are used. The measurement of the acid produced is easy and accurate, and although it is somewhat time consuming, it is made worth while by the accuracy obtained.

Various authors have introduced modifications of this simple method of measuring acid production. Some carry out the titrations by means of a comparator. Others measure the final pH of the medium; and others again carry out an electrometric titration.

(ii) Measurements of the density of the cells present in the cultures. The density of cells present is proportional to the amount of standard vitamin added to the tube. It can be measured with a photoelectric absorptiometer, and the results obtained show good agreement with those found by titration. Measurements of turbidity can be obtained at the end of twenty-four hours' incubation.

(iii) Measurement of the weight of cells formed during incubation. This method is used for the determination of the growth of the mould Neurospora.

Preparation of Samples for Assay.

Preparation of samples for assay often presents difficult problems, as it does in any method of assaying vitamins. There is no general procedure for the extraction of all the vitamin from the sample without removal also of various interfering substances. The methods vary according to the material being assayed, and according to the vitamin under consideration. In the case of urine it is often possible to dilute the urine with water and proceed straight to the assay, but this simple method is inapplicable, of course, to many foodstuffs and other biological materials.

The Phenomenon of Drift.

It is sometimes found that assays carried out on different quantities of extract show poor agreement. The term "drift" is used to describe those cases in which the answers progressively increase or decrease as the aliquots taken are increased in quantity. The phenomenon is due to the presence in the extract of some active substance other than the vitamin that is being assayed. The substance may be stimulant or depressant.

There are three main ways of coping with drift: (*a*) The extract may be treated so as to remove the interfering substances. For example, it is known that various fatty acids stimulate the growth of *Lactobacillus casei* and must therefore be removed from materials that are to be assaysd with this organism. (*b*) The basal medium can sometimes be improved so as to include stimulating substances that are present in the extract. In such cases drift may perhaps be best regarded as a consequence of the use of an inadequate basal medium. (*c*) A third method can be tried in cases in which it is possible to destroy the vitamin that is being assayed, without significantly affecting the stimulant or depressant substances. Extract of the material being analysed can be treated to destroy the vitamin and can then be added to the tubes used for the standard curve. In this way the interfering substances can be introduced in equal amounts to both the tubes containing the known amount of vitamin and those containing the known amount of extract under assay. It would seem that riboflavin, which is so easily destroyed by irradiation, would be ideally suited for assays of this type. We have tried to apply this technique to the assay of wheat products for riboflavin, but the results so far have not been reliable. This general method of overcoming drift, however, deserves more detailed investigation.

Calculation of the Results of Microbiological Assays.

The simplest method of calculating the results is to read off the answers from a graph, as already illustrated in Figure I. This is not the best method, however. Whenever the dose-response curve is linear, or approximately linear, the best results are obtained by calculating the ratio of the slope of the curve for the extract to the slope of the curve for the vitamin. The development of the statistical method of dealing with this problem constitutes one of the important recent advances in microbiological assays. Details of the procedure will be found in the paper by Wood and Finney[12] and a simple account of the general principle is contained in a note by Wood.[11] The method has the great advantage of providing a measurement of the error of the assay. It has also led to a reconsideration of the design of microbiological assays, the most important principle to emerge being that the tubes should be equally divided into a group for the standard curve and a group for the extract. It is pointless to spend more labour in obtaining the standard curve than in obtaining the curve for the extract.

In some cases in which a linear dose-response curve is not obtained, it may be possible to make a simple transformation that renders the curve linear. For example, in certain amino acid assays Wood obtained a straight line by plotting the logarithm of the dose against the logarithm of the response.

Comparison of Microbiological Assay with Other Methods of Assay.

Macrobiological methods of assaying vitamins of the *B* complex are now rarely used in routine practice. The precision of the method is too low for many purposes and the assay is time-consuming. Microbiological methods are quicker. They also have an important theoretical advantage in that each assay is carried out on a large population of organisms. This results in greater precision.

Chemical methods are clearly better than microbiological methods in certain cases, for example, in the assay of thiamine. A vitamin may be assayed microbiologically in the early stages of its discovery and may subsequently be assayed better by chemical means when a specific reaction is studied. There is, however, no reason to believe that chemical assays will invariably prove to be more sensitive, more accurate, simpler, or more specific than microbiological assays. Each case must be considered on its merits.

Appendix.

In this appendix we give certain practical details about the following aspects of the three microbiological assays discussed: (*a*) the storage of the microorganisms required; (*b*) the preparation of the inoculum; (*c*) the composition of the basal media; (*d*) the preparation of individual constituents of the basal media; and (*e*) practical points carrying out the assays.

Storage of Microorganisms.

The organisms used in the tests described are: 1. *Lactobacillus arabinosus* (Number 8014). 2. *Lactobacillus casei* (Number 7469). This has also been referred to as *Lactobacillus helveticus* and *Bacillus casei* ε, but Tittsler *et alii*[10] consider these names incorrect. 3. *Streptococcus fæcalis* (*lactis*) Rogers (Number 9790). These organisms may be obtained from the American type culture collection, Georgetown University Medical School, where they are given the numbers indicated in brackets above. They are also now obtainable from various laboratories throughout the world.

Stock cultures of *Lactobacillus arabinosus* and *Lactobacillus casei* are carried on a yeast-water-glucose-agar medium, which is prepared from the following ingredients: 1 gramme of "Difco" yeast extract, 2 grammes of glucose, 4 grammes of sodium acetate, 2 grammes of agar and sufficient water to bring the volume to 100 millilitres. For *Streptococcus fæcalis* R. one adds 0·25 gramme of dipotassium hydrogen phosphate and 0·5 millilitre of "Plexan" liver extract. The mixture is steamed over a water bath to dissolve the agar. Approximately 10 millilitres of this hot solution are added to test tubes, which are then plugged with cotton wool. The tubes are autoclaved at 15 pounds for 15 minutes, and are allowed to cool in an upright position. They are stored in the refrigerator and will keep more or less indefinitely. On the agar medium, stab cultures of the organisms are grown, and it is usual to maintain one stock culture and two or more "working" cultures for each organism. These are all incubated at 37° C. for twenty-four hours, and are then stored in the refrigerator. The stock cultures are renewed once a month.

Preparation of Inoculum.

The medium used for preparing the inoculum of *Streptococcus faecalis* R. is the same as that employed for carrying the stock culture, except that the agar is omitted. To obtain an inoculum one transfers cells from one of the working cultures of the organism into a centrifuge tube containing about 10 millilitres of the sterile medium supplemented with one or two microgrammes of the appropriate vitamin. This culture is then incubated at 37° C. for 16 to 24 hours. At the end of this time a pin is passed through the cotton wool plug to retain it in position during centrifuging. The culture is then spun down, and the resulting supernatant liquid is removed aseptically by means of a pipette. The cells are suspended in 10 millilitres of sterile isotonic saline or sterile water. The cells are centrifuged and washed with saline twice more, in order to remove any traces of the vitamin it is required to assay. High blanks result if any vitamin is carried over. The final suspension of cells is diluted until it is just barely turbid and this is then used as the inoculum. It can be stored in the refrigerator for use next day if assays are to be made on successive days, but should not be kept for a longer time.

Preparation of Individual Constituents of the Basal Media.

Casein Hydrolysate.—Casein hydrolysate can be obtained from Ashe Laboratories, Limited, 120-122 Victoria Street, London, S.W.1, England. It should always be weighed quickly, as it is very hygroscopic.

l-Cystine Solution.—Five hundred milligrammes of l-cystine are suspended in about 150 millilitres of water. The least possible amount of normal hydrochloric acid required to effect solution is then added and the solution is heated to boiling point. After being allowed to cool, it it made up to 500 millilitres with water. The concentration of this solution is one milligramme per millilitre.

Sodium Acetate.—When the pancreatin digest of casein is made up in the manner described later, there is no need for additional sodium acetate to be added to the folic acid free basal medium.

dl-Tryptophan Solution.—For the nicotinic acid assay the synthetic dl acid should always be used owing to the contamination of the natural l form with nicotinic acid.[1] Four hundred milligrammes of dl-tryptophan are suspended in about 50 millilitres of water. The least possible amount of normal hydrochloric acid required to effect solution is then added and the solution is heated to boiling point. After being allowed to cool it is made up to 100 millilitres with water. The final concentration is four milligrammes per millilitre.

l-Tryptophan Solution.—Five hundred milligrammes of l-tryptophan are suspended in about 25 millilitres of water. The least possible amount of normal hydrochloric acid required to effect solution is added, and the solution is heated to boiling point. After being allowed to cool, it is diluted to 50 millilitres. The concentration is ten milligrammes per millilitre.

Adenine and Guanine Solution.—Fifty milligrammes each of adenine sulphate and guanine hydrochloride are dissolved with heat in 2·5 millilitres of 20% solution of hydrochloric acid; after the solution has been allowed to cool, sufficient water is added to make up the volume to 50 millilitres. The concentration of the solution is one milligramme per millilitre of both adenine and guanine.

Uracil Solution.—Fifty milligrammes of uracil are suspended in 25 millilitres of water, and dissolved by the addition of a minimum quantity of strong ammonia. Sufficient water is added to make up the volume to 50 millilitres. The concentration of the solution is one milligramme per millilitre.

Thiamine Hydrochloride, Pyridoxine Hydrochloride, Calcium d-Pantothenate and Para-aminobenzoic Acid Solutions.—Ten milligrammes of each of these four vitamins are dissolved in separate amounts of 100 millilitres of water. The concentration of the vitamins is 100 microgrammes per millilitre in each case.

Nicotinic Acid Solution.—Twenty milligrammes of nicotinic acid are dissolved in alcohol and are made up to 200 millilitres with alcohol. The concentration is 100 microgrammes per millilitre and this is used as a stock solution for folic acid-free and riboflavin-free basal media. It is diluted with water to give one microgramme per millilitre for the nicotinic acid standard solution. This latter solution should be made up afresh for each assay.

Riboflavin Solution.—Twenty milligrammes of crystalline riboflavin are dissolved in sufficient 0·02 normal acetic acid to make the volume up to 1000 millilitres. This gives a concentraton of 20 microgrammes per millilitre and is the solution used for nicotinic acid-free and folic acid-free basal media. It is diluted to 0·1 microgramme per millilitre with water for use as a standard solution in the riboflavin assay. This dilute solution should be made up afresh for each assay. The concentrated solution is stored in a dark bottle. In the case of this solution, and any

TABLE II

Composition of Three Typical Basal Media.

Ingredient.	Quantity Required for 250 Millilitres of		
	Riboflavin-Free Basal Medium for Assay with *Lactobacillus casei*.[1]	Nicotinic Acid-Free Basal Medium for Assay with *Lactobacillus arabinosus*.[2]	Folic Acid-Free Basal Medium for Assay with *Streptococcus faecalis* R.[3] [4]
1. Casein hydrolysate	—	3·0 grammes.	2·5 grammes.
2. l-cystine	50·0 millilitres.	100·0 millilitres.	100·0 millilitres.
3. Glucose	5·0 grammes.	10·0 grammes.	10·0 grammes.
4. Xylose	0·25 gramme.	0·5 gramme.	—
5. Sodium acetate (anhydrous)	—	10·0 grammes.	10·0 grammes.
6. dl-trytophan solution	—	25·0 millilitres.	—
7. l-tryptophan solution	—	—	2·5 millilitres.
8. Adenine and guanine solution	—	5·0 millilitres.	5·0 millilitres.
9. Uracil solution	—	5·0 millilitres.	5·0 millilitres.
10. Pyridoxine solution	—	1·0 millilitre.	10·0 millilitres.
11. Nicotinic acid solution.	0·125 millilitre.	—	2·5 millilitres.
12. Riboflavin solution	—	5·0 millilitres.	5·0 millilitres.
13. Ca-d-pantothenate solution	0·125 millilitre.	0·5 millilitre.	0·5 millilitre.
14. Thiamine solution	—	0·5 millilitre.	0·5 millilitre.
15. Para-aminobenzoic acid solution	—	0·5 millilitre.	0·5 millilitre.
16. Biotin	—	2·0 millilitres.	2·0 millilitres.
17. Salt solution A	2·5 millilitres.	2·5 millilitres.	2·5 millilitres.
18. Salt solution B	2·5 millilitres.	2·5 millilitres.	2·5 millilitres.
19. Photolysed peptone solution	50·0 millilitres.	—	—
20. Sodium chloride	—	2·5 grammes.	—
21. Pancreatin digest of casein	—	—	15·0 millilitres.
22. Xanthine solution	—	5·0 millilitres.	—

Note.—All water used in the basal media should be glass-distilled. Fifty assay tubes can be made up with 250 millilitres of basal medium.

[1] The pH is adjusted to 6·6 or 6·8 with 20% sodium hydroxide. The volume is then made up to 250 millilitres with riboflavin-free yeast supplement.

[2] The pH is adjusted to 6·6 or 6·8 with 20% sodium hydroxide and the volume is made up to 250 millilitres with water.

[3] The pH is adjusted to 7·0 or 7·2 with 20% sodium hydroxide and the volume is made up to 250 millilitres with water.

others containing riboflavin, exposure to light is carefully avoided, as riboflavin is destroyed by light.

Biotin Solution.—The contents of an ampoule containing 25 microgrammes of the free acid are made up to 250 millilitres with water. The concentration is 0·1 microgramme per millilitre of biotin and the solution will maintain its activity for about three months.

Salt Solution A.—Twenty grammes of di-potassium hydrogen phosphate and 25 grammes of potassium dihydrogen phosphate are dissolved in water and the volume is made up to 250 millilitres.

Salt Solution B.—Ten grammes of magnesium sulphate (heptahydrate), 0·5 gramme of sodium chloride, 0·5 gramme of ferrous sulphate (heptahydrate) and 0·5 gramme of manganous sulphate (tetrahydrate) are dissolved in water. Five drops of concentrated hydrochloric acid are added in order to prevent precipitation of the salts, and the volume is made up to 250 millilitres with water.

Photolysed Peptone Solution.—Forty grammes of "Difco" Bacto peptone are dissolved in 250 millilitres of water, and 20 grammes of sodium hydroxide, also dissolved in 250 millilitres of water, are added. The solutions are mixed in a 25 centimetre crystallizing dish, and are exposed for six to ten hours to the light from a 100 watt bulb which is fitted with a reflector and placed at a distance of 30 centimetres. This irradiation is to ensure the complete destruction of all the riboflavin in the peptone. The solution is allowed to stand at room temperature for 14 to 18 hours, and is then neutralized with glacial acetic acid (about 27·9 millilitres). Seven grammes of anhydrous sodium acetate are then added, and this final solution is made up to 800 millilitres with water.

Pancreatin Digest of Casein.—Pancreatin digest of casein is made up according to a modification of the method of Roberts and Snell.[4] Sixty grammes of vitamin-free casein are gradually added with shaking to two litres of 0·8% sodium bicarbonate at 37° C. To the suspension thus obtained, 300 milligrammes of pancreatiin suspended in 15 to 20 millilitres of water are added, and are well mixed with the casein suspension. The mixture is covered with a thin layer of toluene and is incubated for eight days at 37° C. The mixture is shaken several times a day to ensure complete digestion of the casein by the pancreatin. After incubation, the resulting solution is heated in gently flowing steam in an autoclave for thirty minutes to remove the toluene. During this time, great care must be taken to avoid loss of the digest by frothing. After the digest has been allowed to cool to room temperature, it is adjusted to pH 6·0 by the addition of glacial acetic acid (about 3·5 millilitres), and is filtered through ordinary funnels. To the filtrate 60 grammes of activated charcoal ("Norit" A or "Darco" G60) are then added and the mixture is stirred for thirty minutes. Filtration is again performed, ordinary funnels being used. The filtrate, which now contains small amounts of colloidal charcoal, is adjusted to pH 3·8 with glacial acetic acid (about 35 millilitres) and then 24 grammes of activated charcoal are added. The digest is stirred for 30 minutes, and then filtered. The residue from each filtration is washed with 50 to 70 millilitres of water, and these washings are added to the filtrate. These charcoal treatments are to remove traces of the various vitamins, especially folic acid, which are present in the initial digest. The final clear filtrate is diluted to 2·4 litres. One millilitre of this solution contains approximately 25 milligrammes of casein.

Xanthine Solution.—Fifty milligrammes of xanthine are suspended in about 25 millilitres of water, and a minimum amount of strong ammonia is added to effect solution. The volume is then made up to 50 millilitres with water. The concentration is one milligramme per millilitre.

Yeast Supplement (Riboflavin-Free).—One hundred grammes of "Difco" yeast extract are dissolved in 500 millilitres of water and 150 grammes of basic lead acetate are added. The pH of the mixture is adjusted to approximately ten with strong ammonia and the precipitate is allowed to settle, preferably overnight, and is then filtered off. The filtrate is then barely acidified with glacial acid, and hydrogen sulphide is passed into it until all the excess lead is precipitated. The lead sulphide is, in turn, filtered off and the volume is adjusted to one litre.

Standard Solution of Folic Acid.—Five milligrammes of crystalline folic acid are dissolved in 250 millilitres of water, and the volume is adjusted to 500 millilitres with alcohol. The concentration is 10 microgrammes per millilitre, and this is diluted with water to 0·5 millimicrogramme per millilitre for the standard solution. The latter should be made up afresh for each assay. The stock solution will maintain its activity for three months, if it is protected from light.

Storage of Solutions.—It is usual to store all these solutions under toluene in the refrigerator. Even so, moulds sometimes grow in them and they should therefore be inspected before use.

Practical Points in the Carrying Out of the Assays.

Riboflavin.—In the older method of carrying out the test, the standard curve was drawn up by measuring the response to the following amounts of riboflavin solution: 0·0, 0·5, 1·0, 1·5, 2·0 and 2·5 millilitres of a solution containing 0·1 microgramme per millilitre. The unknown solution was assayed at three or four levels, the aim being to pick three levels which fell within the above range. Duplicate or triplicate sets of tubes were used for each level of the standard and of the unknown. A better method, however, is to concentrate on the accurate determination of four levels, two for the standard and two for the unknown. These are, in the case of the standard, 0·05 and 0·20 microgramme. The levels for the unknown are selected to correspond to these, and, to ensure this, a preliminary analysis may be necessary if the investigator is working with unfamiliar material. The results are calculated by the "slope-ratio" method. The best design for these assays is the "common zero-five point" assay.[12]

The autoclaving of this particular medium can be carried out for 15 minutes at a pressure of 15 pounds to the square inch. Great care must be taken, however, to avoid exposure of the warm tubes to light. Even in the cold, riboflavin in solution is readily destroyed by ultraviolet light, so that the work must be done in dim artificial light.

The incubation is carried out at 37° C. for 72 hours. Uniformity of temperature is important. As an illustration of this we may quote results obtained when we placed sets of tubes containing equivalent amounts of basal medium and riboflavin in the following sites on the upper and lower shelves of a commercial electric incubator: lower centre, upper right posterior, lower right anterior, lower left posterior, lower right posterior, lower left anterior, upper centre, upper right anterior, upper left posterior and upper left anterior. The amounts of deci-normal acid produced in these sites were respectively: 9·1, 7·7, 7·4, 7·1, 7·0, 6·8, 6·8, 6·6, 6·6, and 6·1 millilitres.

In duplicate titrations there is rarely a greater difference than 0·3 millilitre.

Nicotinic Acid.—The general design for the assaying of nicotinic acid is similar to that used for the assay of riboflavin. The amounts of niacin used in determining the standard curve are: 0, 1·0, 2·0, 3·0, 4·0 and 5·0 millilitres of a solution containing 0·1 microgramme per millilitre. The portion of the curve between the abscissæ at 0·2 and 0·4 microgramme approaches a linear form so that the "four-point" or "common zero-five point" assay can be used in the case of niacin as well as riboflavin. The basal medium darkens if autoclaved for more than ten minutes at ten pounds to the square inch. The tubes are incubated at 30° C. for 72 hours.

Folic Acid.—We have not seen any details of the type of standard curve obtained in the assay of folic acid when the Ruegamer medium is used. Our own experience is that, in the range from 0 to 1·0 millimicrogramme, a curve is obtained which rises rapidly at first, then slowly, and then rapidly once more. This curve can be determined accurately only if about five tubes are set up at each level, for the discrepancy between replicates is greater than in the other assays. At the present time we determine ten points on the standard curve and ten on the curve for the unknown.

The autoclaving is done at ten pounds per square inch for ten minutes. The tubes are incubated at 37° C. for only 18 hours. Throughout the assay one must take strict precautions against exposure of the solutions to light. The unusual type of curve obtained makes the standard statistical methods inapplicable. If the axes are rotated through 90°, however, the curve becomes a normal sigmoid and can be evaluated by the method of probit analysis. The process is tedious and unsuitable for routine work. We are persevering with it at this stage because other methods of assay have, in our experience, been unsatisfactory.

Acknowledgements.

One of us (C.W.) began work on microbiological assays in the Australian Institute of Anatomy, Canberra, and is indebted to Dr. F. W. Clements for the facilities he made available there. We wish to thank the Medical Research Council of Great Britain for a grant towards the work on folic acid.

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THE INCIDENCE OF PARASITIC INFECTIONS IN NEW SOUTH WALES.

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PART I: INCIDENCE OF INTESTINAL PROTOZOA IN RECRUITS OF THE AUSTRALIAN ARMY.

DURING the 1939-1945 war the soldiers passing through the General Details Depot in Sydney provided an unusual opportunity for a survey of the incidence of intestinal protozoa in the Australian population; this was carried out from December, 1941, to November, 1943. The primary object was to get some idea of how many people in the community were passing *Entamœba histolytica* cysts. Amœbic dysentery is rare in Australia, and it is of some interest to see if the asymptomatic carrier is also uncommon.

At that time the only published figures were those of Maplestone (1920) and of Willis (1923), who carried out surveys on people living in the Townsville district of North Queensland.

Materials and Methods.

The persons examined were all males of military age, usually about nineteen or twenty years of age. In the great majority of cases they had been living in New South Wales before enlistment, but some were from other States, including the tropical parts of Queensland and the Northern Territory. An Australian army hygiene unit, attached to the depot, attended to the collection of the specimens and arranged for their delivery to the laboratory. A senior non-commissioned officer of this unit supervised the collection and labelling of specimens, and filled in a form giving particulars which might be of value in the analysis of results. In addition to the names and ages of the soldiers he recorded particulars of their places of residence and the length of time during which they had lived there, and also whether they had any history of diarrhœa or dysentery.

The specimens were delivered to the laboratory on the day of collection and at the rate of about ten per day. They were examined on the day of receipt or the following day. Only one normally passed stool was examined from each person, except in those cases in which the identification of the cysts was in doubt, when a further specimen was obtained if possible. The method of examination was by direct smear in eosin (or physiological saline) and iodine solutions. One drop of eosin and one of iodine solution were placed on a slide, a small portion of fæces was emulsified first in the drop of eosin and then in the drop of iodine, and the two smears were covered with a square 22-millimetre coverslip. The preparation was searched with a low-power objective (16 millimetres), followed by a high dry objective (four millimetres) for ten to fifteen minutes before being declared "negative". If protozoa which could not be identified were seen in this preparation, a thin iodine film was examined with an oil immersion lens. Also, if trophozoites were thought to be present, a preparation in physiological saline was examined. Finally, if necessary, films were fixed and stained with iron hæmatoxylin.

Some specimens were examined by the zinc sulphate flotation method as well as by direct smear. The method used differs slightly from Faust's (1939) technique and is as follows:

A small portion of fæces the size of a pea is emulsified in about 20 millilitres of tap water. If the stool is hard to emulsify it is soaked for twenty minutes and then shaken with glass beads. The emulsion is strained through wire gauze (14 holes to the inch) into a centrifuge tube and spun for two minutes at 2500 revolutions per minute. The supernatant fluid is poured off and replaced by zinc sulphate solution (specific gravity 1·18), and the tube is shaken for a quarter of a minute, and then centrifuged for four minutes at 2500 revolutions per minute. Two to three loopfuls of the surface film are removed by means of a platinum loop about 0·5 centimetre in diameter and added to a drop of iodine on a slide. Finally a 22 millimetre square coverslip is dropped on and the edges are sealed with petroleum jelly.

When this method was used the number of cysts seen per coverglass preparation in "positive" specimens was usually about ten to twenty times that seen in the direct smear.

Several members of the staff of the parasitology department assisted in the microscopic examination of stools; we checked their work by means of parallel examinations until they had proved their efficiency in the recognition of infections.

Results.

The incidence of intestinal protozoa in those persons who had spent all their life in Australia is shown in Table I.

The number of double infections was 42, made up as follows: *Entamœba histolytica* (large race) and *Endolimax nana*, 3; *Entamœba histolytica* (large race) and *Giardia lamblia*, 1; *Entamœba histolytica* (small race) and *Entamœba coli*, 3; *Entamœba coli* and *Endolimax nana*, 20; *Entamœba coli* and *Giardia lamblia*, 8; *Entamœba coli* and *Chilomastix mesnili*, 1; *Endolimax nana* and *Giardia lamblia*, 6.

The number of triple infections was eight, as follows: *Entamœba histolytica* (small race), *Entamœba coli* and *Giardia lamblia*, 3; *Entamœba histolytica* (large race), *Entamœba coli* and *Giardia lamblia*, 1; *Entamœba histolytica* (large race), *Entamœba coli* and *Endolimax nana*, 2; *Giardia lamblia*, *Entamœba coli* and *Endolimax nana*, 1; *Giardia lamblia*, *Iodamœba butschlii* and *Endolimax nana*, 1.

There was one quadruple infection with *Entamœba histolytica* (both races), *Entamœba coli* and *Giardia lamblia*.

TABLE I.

Incidence of Intestinal Protozoa in Soldiers who had Never Left Australia; 2,365 Persons Examined Once Only by Direct Smear of Fæces.[1]

Parasite.	Positive Result.	
	Number.	Percentage.
Entamœba histolytica—		
Large race	16	0·68 } 1·31
Small race	15	0·63 }
Entamœba coli	212	8·96
Endolimax nana	134	5·66
Iodamœba butschlii	3	0·13
Dientamœba fragilis	1	0·04
Giardia lamblia	165	6·98
Trichomonas hominis	1	0·04
Chilomastix mesnili	2	0·08
Not identified	4	0·17

[1] "Negative" specimens, 1873 (79·20%).

Trophozoites, either alone or together with cysts, were seen in some cases: *Entamœba coli*, three times; *Endolimax nana*, five times; *Giardia lamblia*, three times; *Chilomastix mesnili*, once.

Only one normally passed stool from each person was tested, the method used being examination of a direct smear. Many workers (for example, Svensson, 1935) have shown that the examination of a loose stool, obtained by a saline purge, gives much better results than examination of the normal stool; but it was impossible to arrange for the routine collection of such material. In particular, *Dientamœba fragilis* and *Trichomonas hominis*, which do not form cysts, are likely to be missed in formed stools; so are *Enteromonas hominis* and *Balantidium coli*.

TABLE II.

Incidence of Intestinal Protozoa in Soldiers whose Whole Life had not been Spent in Australia; 210 Persons, Examined Once Only, by Direct Smear of Fæces.[1]

Parasite.	Positive Result.	
	Number.	Percentage.
Entamœba coli	15	7·14
Endolimax nana	13	6·19
Giardia lamblia	13	6·19
Not identified	1	0·48

[1] Number of "negative" specimens, 171 (81·4%).

Table II gives the results obtained from those persons who had been born outside Australia or had left the country at any time. Actually, in most cases, they had been continuously resident in Australia for some years prior to the examination.

The number of double infections was three, made up as follows: *Entamœba coli* and *Endolimax nana*, 2; *Entamœba coli* and *Giardia lamblia*, 1.

Specimens from 286 persons were examined by the zinc sulphate flotation method as well as by the direct smear method. Protozoal cysts were found in 94 of these specimens by one or both methods, 90 giving positive results by the flotation method, but only 76 by the direct smear method. Details of these results are set out in Table III. The few specimens that were found "positive" by the direct smear method but "negative" by the zinc sulphate flotation method contained cysts and not trophozoites, so that the failure of the zinc sulphate method in these cases was not due to this cause.

The gain in positive results by the use of the zinc sulphate flotation method was of the order of that found by Faust *et alii* (1939) and more recently by Elsdon Dew (1947). The gain in positive results is shown below; the ratio is obtained by dividing the number of positive results found by the zinc sulphate flotation method by the number of positive results found by the direct smear method.

TABLE III.

Comparison of Results Obtained on Examination of 286 Specimens by Direct Smear Method and Zinc Sulphate Flotation Method.

Parasite.	Number "Positive" by Direct Smear Method.	Number "Positive" by Zinc Sulphate Flotation Method.	Number "Positive" by Direct Smear Method and "Negative" by Zinc Sulphate Flotation Method.	Number "Negative" by Direct Smear Method and "Positive" by Zinc Sulphate Flotation Method.
Entamœba histolytica	2	3	0	1
Entamœba coli	35	52	0	17
Endolimax nana	24	26	3	5
Iodamœba butschlii	2	2	0	0
Giardia lamblia	23	27	1	5

The differences between our results and those of Elsdon Dew for *Iodamœba butschlii* and *Giardia lamblia* are probably due to the small numbers involved. In the case of *Endolimax nana*, whose cysts are rather difficult to identify without staining with hæmatoxylin, we sometimes had trouble in identifying the cysts after zinc sulphate flotation, which tends to distort them.

Discussion.

The true incidence of the various fæcal protozoa must be higher than the figures given in Table I. Several workers have tried to find the proportion of infections that can be demonstrated by examining only one formed stool from each person. One of the most valuable of these studies is that of Svensson (1935), who concluded that the demonstrability of infections, whether by the examination of one or even of six formed stools, varies from population to population, being higher where the incidence of infection is higher. Hence it is impossible to use the demonstrability found for one population to calculate the "true" incidence in another, and surveys of different populations, unless based on the impossible ideal of an exhaustive examination of each person, are not strictly comparable. However, Svensson makes a partial exception in the case of *Entamœba histolytica*. Her figures support Dobell's (1921) estimation that approximately one-third of existing infections are discovered by examining only one stool per person. This conclusion is based on work on such diverse populations as mental asylum

TABLE IV.

Ratio of Positive Results Found by Zinc Sulphate Flotation Method as Compared with Direct Smear Examination.

Parasite.	This Series.	Faust's Series.	Elsdon-Dew's Series.
Entamœba histolytica	$\frac{3}{2}=1·5$	$\frac{65}{31}=2·1$	$\frac{172}{98}=1·8$
Entamœba coli	$\frac{52}{35}=1·5$	$\frac{118}{72}=1·6$	$\frac{203}{119}=1·7$
Endolimax nana	$\frac{26}{24}=1·1$	$\frac{110}{68}=1·6$	$\frac{104}{33}=3·2$
Iodamœba butschlii	$\frac{2}{2}=1·0$	$\frac{6}{3}=2·0$	$\frac{52}{9}=5·9$
Giardia lamblia	$\frac{27}{23}=1·2$	$\frac{34}{24}=1·4$	$\frac{15}{3}=5·0$

patients in Sweden, soldiers in England, and Chinese in Peking. It is interesting to note that Marsden and Fairfield Smith (1946), dealing with prisoners of war who had suffered from amœbic dysentery some time during the previous two years, and among whom the overall rate of *Entamœba histolytica* cyst-passers was 30·2% $\left(\frac{307}{1015} \times 100\right)$ found 36·5% of their positive results on examination of the first stool. In most cases they examined six stools from each person—a procedure that in their estimation (and also in that of other workers) would not detect all the cyst-passers. The figure of 36·5% must therefore be somewhat high and the proportion of positive results obtained by the examination of one stool is, once again, somewhere about one-third.

From the above it appears that the proportion of the adult male population in New South Wales passing *Entamœba histolytica* cysts is about 3%.

The incidences of cysts reported here are usually lower than those reported by Maplestone (1920) and by Willis (1923), who carried out a survey on the population in Townsville and its surrounding district, an area which lies within the tropics. It is interesting that the incidence of *Entamœba histolytica* in the urban population was 1%—approximately the same figure that we have found. The stools came from subjects of both sexes and all ages, and were those sent in for examination for hookworm eggs. Only one examination, by the direct smear method, was made on each specimen. These results, set out by age groups as percentages of subjects infected with the different species, are given in Table V.

TABLE V.
Townsville District.
(Maplestone, 1920.)

Ages in Years.	Number of Subjects Examined.	Percentages Infected.		
		Entamœba histolytica.	*Entamœba coli.*	*Giardia lamblia.*
1 to 5 ..	48	4·2	4·2	22·9
6 to 10 ..	55	5·5	12·7	23·6
11 to 15 ..	41	9·75	41·5	22·0
16 to 20 ..	39	5·1	23·1	10·2
21 to 30 ..	72	6·9	29·2	4·2
31 to 40 ..	57	1·75	26·3	8·8
Over 40	117	1·7	23·9	5·1
Totals ..	429	4·4	23·1	12·1

TABLE VI.
Townsville Urban.
(Willis, 1923.)

Ages in Years.	Number of Subjects Examined.	Persons Infected (Percentages).			
		Entamœba histolytica.	*Entamœba coli.*	*Iodamœba butschlii.*	*Giardia lamblia.*
Under 6 ..	96	0	5·2	0	36·5
6 to 18 ..	155	0	20·0	3·2	25·8
19 to 40 ..	143	2·8	20·3	0·7	4·9
Over 40 ..	46	2·2	10·9	2·2	4·1
Totals ..	440	1·1	15·9	1·6	19·1

No infections with *Endolimax nana* were found in either of these two Townsville surveys. Maplestone's figures for infections by age groups have been taken from his Table IV, which shows only the infections with *Entamœba histolytica, Entamœba coli* and *Giardia lamblia* of persons living in private houses. Seventy-one children from the Townsville Orphanage were also examined and were included in the total figures of 500 examinations in his Table I; we have excluded them from consideration because groups from institutions (orphanages, asylums *et cetera*) usually have rates of infection higher than those of the general population.

Maplestone also found cysts of *Chilomastix mesnili* in 2·2% and of *Iodamœba butschlii* in 1% of his examinations.

Figures for the incidence of *Entamœba histolytica* cysts in Australian troops have recently been given by Andrew (1946) (quoting work carried out by Major H. O. Lancaster) for soldiers with service in the Middle East, with service in New Guinea, and with home service only. Of 155 persons in the last group, 3·2% gave positive results. Each person was examined once, the method being by direct examination of a smear in eosin and iodine (personal communication from Major Lancaster).

In Canada, Williams (1946) found, as a result of three examinations on alternate days, a 2% incidence of *Entamœba histolytica* cysts in recruits to the armed forces; these men had never left Canada.

Dobell (1921) summarized the various reports available to that date on the incidence of *Entamœba histolytica* in persons who had never left Britain. Of 3146 persons whose fæces were examined by the direct smear method, 3·4% were found to be infected. The great majority of the persons were examined only once.

In the United States, Boeck and Stiles (1923) found 3·5% of 2584 soldiers, with home service only, to be infected with *Entamœba histolytica*; the average number of examinations per subject, which were by the direct smear method, was 1·3.

Craig (1944) has gathered the data from 40 surveys of the general population in the United States; of 118,156 persons examined by various methods and with varying degrees of thoroughness, 8·1% were infected with *Entamœba histolytica*. Faust (1942) pointed out that most of these data have been derived from a single fæcal examination, and that if more stools per person were examined and improved methods were used the incidence might be as high as 20%. Incidentally, certain groups, such as college and university students, have a much lower infection rate.

The incidence of persons infected with *Entamœba histolytica* in New South Wales seems to be lower than that found generally in Britain and the United States of America. A valuable discussion on the importance of such symptomless carriers of *Entamœba histolytica* took place at a meeting of the Royal Society of Tropical Medicine and Hygiene, and is published in the Society's transactions (Wenyon *et alii*, 1947).

It will be noticed that in Table I we have shown the large and small races of *Entamœba histolytica* separately, as it is now generally agreed that two distinct races exist, one producing cysts of the ordinary type, over 10μ in diameter, and the other smaller cysts under 10μ in diameter (see Wenyon, 1947). The small race is thought by some to be a separate species. Moreover, the pathogenicity of the small race is in doubt. For instance, Wenyon (1947) makes the following statement.

> There do not appear to have been any satisfactory records of frank amœbic dysentery in man caused by the small race of *E. histolytica*. We must suppose that the tendency to damage the intestinal wall is much less in the case of the small race than in the large, so that actual dysentery rarely if ever occurs.

Acknowledgements.

We wish to acknowledge the help of Mr. P. Byrnes, Mr. A. Grimmo and Mr. G. Merritt, who assisted in the examination of these specimens.

Summary.

The incidences of intestinal protozoa in 2365 soldiers (mainly recruits) who had never been outside Australia, as determined by the examination of a single specimen from each man by the direct smear method, are set out in Table I.

PART II: INCIDENCE OF INTESTINAL PROTOZOA AND WORMS IN A GROUP OF NEW SOUTH WALES CHILDREN.

Material and Methods.

The group of children examined were inmates of the Royal Alexandra Hospital for Children and came mostly from the suburbs of Sydney, the remainder being from country towns and rural areas of the State. Their ages ranged from fourteen days to fourteen years.

The specimens of fæces were collected by the hospital staff and were examined within forty-eight hours. The methods used in examining the specimens for protozoal cysts were the same as those described in Part I. Worm infestations were also looked for, the direct centrifugal flotation method of Clayton Lane (1923) being used.

Results.

The incidence of protozoal cysts found is given in Table VII. The results are based on a single examination of a normally passed stool of each subject. Approximately equal numbers of boys and girls are included in the table.

No protozoa were found in 81% of the 416 specimens examined. Seventy-five children under two years of age are included in Table VII, but the only protozoal infections in this group were seven cases of *Giardia lamblia* infection.

TABLE VII.

Incidence of Protozoal Cysts in 416 New South Wales Children.

Parasite.	Percentage of Positive Findings According to Age Groups.	
	0 to 5 Years. (220 examined.)	6 to 14 Years. (196 examined.)
Entamœba histolytica—		
Large race	0·0	1·0
Small race	0·4	0·0
Entamœba coli	2·7	9·3
Endolimax nana	0·4	2·4
Dientamœba fragilis	0·4	0·5
Giardia lamblia	13·9	8·8
Chilomastix mesnili	1·3	2·4
Not identified	0·9	0·5

There were eight double infections, as follows: *Entamœba coli* and *Giardia lamblia*, 3; *Entamœba coli* and *Chilomastix mesnili*, 3; *Endolimax nana* and *Giardia lamblia*, 1; *Giardia lamblia* and an undiagnosed cyst, 1.

Three triple infections were found: *Entamœba histolytica* (large race), *Endolimax nana* and *Giardia lamblia*, 1; *Entamœba histolytica* (small race), *Entamœba coli* and *Giardia lamblia*, 1; *Entamœba coli*, *Endolimax nana* and *Chilomastix mesnili*, 1.

The only quadruple infection was one with *Entamœba histolytica* (large race), *Entamœba coli*, *Endolimax nana* and *Giardia lamblia*.

Four hundred and ten of the specimens were examined by Clayton Lane's direct centrifugal flotation method with the results set out in Table VIII.

TABLE VIII.

Incidence of Intestinal Worms as Shown by Clayton Lane's Direct Centrifugal Flotation Concentration Technique; 410 Persons Examined.

Parasite.	Number of Positive Results.
Enterobius vermicularis	13
Trichocephalus trichiurus	1
Trichostrongylus colubriformis	1

The true incidence of *Enterobius vermicularis* is of course much higher than the figure given. Special methods for the detection of eggs, such as swabbing the anal folds on a number of occasions, are necessary to get some approximation to the true number of infections. The *Trichostrongylus* infection has already been reported by Heydon and Bearup (1939).

Discussion.

A low incidence of infection with intestinal protozoa is to be expected from the results already given for the adult population. Infections with *Giardia lamblia* were more common in children than in adults—a result similar to that found in surveys elsewhere. Faust (1933) in New Orleans, and Meleney, Bishop and Leathers (1932) in Tennessee, found the incidence to rise rapidly in early childhood and then to fall gradually until in young adults it was about one-third of the highest incidence. The incidence of people passing amœbic cysts showed a gradual rise with age up to the second decade and then remained stable.

Figures for the incidence of protozoal cysts in children living in tropical Australia, as found by Maplestone (1920) and Willis (1923) are set out in Tables V and VI. When these are compared with Table VII it will be seen that the children living in the tropics have a higher incidence of protozoal infections—a common finding for populations living in the tropics as compared with those living in a temperate zone.

Summary.

1. The incidences of intestinal protozoa in 416 children in a Sydney hospital, as determined by the examination of a single specimen by the direct smear method, are given in Table VII.

2. The incidences of intestinal worms in 410 of these children, as found by Lane's direct centrifugal flotation concentration method for eggs, are given in Table VIII.

ACKNOWLEDGEMENT.

This contribution is published by permission of the Director-General of Health, Commonwealth Department of Health, Canberra.

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SPHENOIDAL SINUSITIS IN ADULTS.[1]

By CLIVE M. EADIE,
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WHEN considering the ætiology of sphenoidal sinusitis in adults we bear in mind that there are two groups of cases. The first group includes those cases in which the mucosa lining these sinuses is inflamed as a result of an infection affecting the whole of the mucosa of the upper respiratory tract. This is seen in such diseases as influenza, measles, scarlet fever, cerebro-spinal meningitis, *et cetera*. The second group consists of those cases in which there are localized inflammatory areas affecting the sphenoidal sinus mucosa, the rest of the sinus mucosa being normal.

With regard to the first group, normally the resistant powers of the mucous membrane are sufficient to overcome such an infection and the mucosa of the sinus returns to normal. We do notice in certain of these cases that the brunt of the attack is borne, or rather the signs of resistance to the infection are more pronounced, in certain particular sinuses than in others; the anterior group may be more affected than the posterior group and *vice versa*. Now, why is this the case? Is it not possibly associated with the question of adequate ventilation and drainage of the sinuses? Then again, we often notice that in certain cases the sphenoidal sinus remains infected after the rest of the acute upper respiratory disease has cleared up. The maxillary antrum often remains thus infected also; but we are not concerned with this sinus, except in so far as it will throw light on to the reason why the sphenoidal sinus remains infected.

We must consider the natural provision made by Nature to combat such infection and to restore the affected structures to their normal state. This leads us to consider, firstly, what keeps the mucosa of these sinuses in a perfectly healthy state, and on the other hand, what leads to their lack of resistance when the attack occurs. Again one would suggest adequate ventilation and drainage and satisfactory general health. Here we must bear in mind the fact that in the nose there is produced a secretion which is apparently bactericidal. Organisms are destroyed, and the upper meatuses and the nasal sinuses are normally sterile. Anything that interferes with the action of this bactericidal secretion on the invading organisms will militate against recovery from the infection.

We must also bear in mind that early in childhood infection of these sinuses may occur and the seed is laid for future trouble throughout life. It is probable that the nasal sinuses are infected through the maternal passages.

The general health of the patient affects the condition of the sinus mucosa and especially the secretions from the glands in the mucosa. Poor general health makes a patient prone to sinusitis, and I would suggest that many terminal infections lead to inflammation of the sinus mucosa with the production of pus if sufficient local resistance is left, or if not, then only of thin serous fluid. I have often observed the latter to be present *post mortem* in the sphenoidal sinuses when patients have died from other debilitating diseases.

Referring to normal ventilation and drainage, I would particularly stress the word "normal", not "free", because we often encounter cases in which the nasal passage on one side is twice as patent as that on the other, and yet it is the sinus on the side of the greater airway that remains infected, the sinus on the narrower side remaining free of infection, or returning to normal after the acute inflammation has subsided. Nature here indicates to us how we should plan our operative interference; surely to leave a wide open space leading directly into the sphenoidal sinus is bad surgery; our endeavour is to correct defects in order that Nature may bring about a cure.

One may ask, what is normal ventilation and drainage? Here I must admit that I find the question difficult to answer.

We can only from our clinical observations correlate certain conditions generally found in the nasal passages when the sphenoidal sinuses are or are not infected, and observe the result on such infection by the correction of these apparently abnormal conditions.

This leads us to consider as ætiological entities such things as (i) posterior septal spurs, (ii) deviated nasal septa, (iii) nasal polypi, (iv) the position of the sphenoidal ostium and its size, (v) the presence or not of pouches, (vi) hyperplastic conditions of the mucosa of the spheno-ethmoidal recesses and (vii) associated infected lymphoid tissue of the naso-pharynx and oro-pharynx.

With regard to hyperplastic conditions of the mucosa of the spheno-ethmoidal recesses, a posterior ethmoidal cell infection may be the cause of this hyperplasia and lead to sphenoidal sinusitis.

With regard to the presence of associated infected lymphoid tissue of the naso-pharynx and oro-pharynx, generally one considers that these are secondarily infected from the sinusitis. But when this tissue has been infected from, for instance, infected teeth, is it not probable that via the lymphatic channels the sphenoidal sinus mucosa may not also become infected? There have been instances of the clearing up of sinusitis by the removal of septic tonsils and septic teeth.

Before leaving the question of ætiology I should like to suggest that the effect of breathing such impure atmospheres as we have developed in our cities today must come under serious consideration. This certainly is a real problem, and must have a considerable bearing on the mental outlook of the present and future generations.

DIAGNOSIS OF SPHENOIDAL SINUSITIS.

Symptoms.

The symptoms associated with sphenoidal sinusitis may be considered as being due to the inflamed sinus mucosa itself, to involvement of adjacent structures, and to the passage of the actual discharge from the sinus.

Amongst those usually complained of, headache is frequent; this is usually occipital and suprafrontal, sometimes vertical. When an acute empyema is present, a severe throbbing pain in the centre of the head is often noted. Paræsthesia of the scalp, such as a feeling of worms moving under the skin, is sometimes a complaint. Pain behind the eyes and a feeling of pressure pushing the eyeballs forward are usually present.

Symptoms due to involvement of adjacent structures vary from endocrine disorders caused by affection of the pituitary gland to neuralgias of the related nerves.

Varying degrees of mental dysfunction, such as lack of concentration and poorness of memory, often occur. Neurasthenic symptoms are often noted in association with chronic cases, and in acute cases those of meningitis and meningismus.

Amongst other frequently occurring symptoms we note disordered vision, asthenopia, vertigo and tinnitus. Loud cracking noises are heard in the head; these I have actually heard, and I noted their disappearance after washing out the affected sphenoidal sinus.

Symptoms due to actual discharge from the sinus are associated with a feeling of stuffiness at the back of the nose and difficulty in nasal breathing, and of being unable to clear the nasal passages by blowing the nose.

Fullness of the ears and post-nasal dropping and stiffness in the back of the neck are also present.

The degree of such symptoms, of course, depends on the acuteness or otherwise of the infection. In acute cases the throat is often extremely painful with a feeling of constriction. Swallowing is difficult. An irritating cough is usually present, often occurring in spasmodic attacks and particularly bad when the patient rises in the morning. Huskiness of the voice is common and likewise dyspepsia.

Signs.

During the usual routine ear, nose and throat examination the following signs are associated with the presence of sphenoidal sinusitis. We shall need to distinguish between acute sinusitis and chronic sinusitis.

[1] Read at a meeting of the Section of Oto-Rhino-Laryngology, Australasian Medical Congress (British Medical Association), Sixth Session, Perth, August, 1948.

Acute Infection.

The mucosa on the posterior wall of the oro-pharynx is red and congested and often has a glazed appearance—as if coated with a layer of varnish; later actual yellow pus is noted. The lateral pharyngeal bands may show associated redness, but pus is not usually noted here, as is the case with maxillary antral suppuration. The tonsils are not infected to any great extent, though acute tonsillitis may follow as the sphenoidal sinusitis passes off. The posterior part of the tongue is coated, often having the appearance of wet chamois leather.

Inspection of the naso-pharynx reveals much redness and swelling of the mucosa. The lymphoid tissue is much inflamed. Yellow spots may be present, such as one sees on the faucial tonsils in acute follicular tonsillitis. Usually much yellow pus is present on the roof and extending down into the fossa of Rosenmüller, and so over the cushion of the Eustachian tube. A distinct yellow membrane may be present, resembling that seen in diphtheria. The arch of the posterior choana is red, and pus is often seen to be present on the side of the affected sinus. The posterior ends of the middle turbinates are swollen and red.

If the condition is an acute exacerbation of a chronic infection, œdematous or polypoid membrane is often seen high up in the arch with yellow pus coming through.

There is not usually pus on the roof of the soft palate tracking along and down the lateral pharyngeal bands, as is seen in maxillary sinus suppuration.

Anterior rhinoscopy reveals only some redness of the anterior ends of the turbinates, and there is not much swelling, if any.

On spraying the nostrils with 2% cocaine solution, or even without, one notes some yellow pus far back in the olfactory cleft towards the anterior wall of the sphenoid.

In the case of a widely patent nasal passage, the sphenoidal ostium may be seen, and serous fluid or pus is noted pulsating through.

Examination of the ears as a rule reveals no abnormality.

Chronic Infection.

In cases of chronic infection the picture of the posterior oro-pharyngeal mucosa is like that of chronic granular pharyngitis. Chronic mucopus is often present. Examination of the naso-pharynx also reveals hyperplasia of the mucosa. Often a large piece of mucopus is adhering to the posterior wall and extending forwards on the vault. Similar changes are present in the fossa of Rosenmüller. Polypi are often present in the arch of the posterior choana, extending down to the level of the posterior end of the middle turbinate. The "swell" bodies on the posterior edge of the nasal septum are generally hypertrophied. Anterior rhinoscopy reveals chronic mucosal changes with enlarged blood vessels on the anterior sphenoidal wall, running down to the choanal arch. A polypus may be noted at the ostium. The use of the long-bladed Killian's nasal speculum enables us more readily to examine this region.

X-ray films are of great value in diagnosis. These should be taken in different planes, and a consultation between the radiologist and rhinologist is of distinct advantage. In practice one feels that a positive X-ray report is of definite value, but a negative report does not altogether eliminate the possibility that a sphenoidal sinusitis may be present. Proetz's displacement method associated with lipiodol and X-ray films is often of much value.

Sphenoidal Lavage.—Sphenoidal lavage may be carried out firstly through the natural ostium, by means of a cannula and a Higginson's syringe, or a "Record" syringe after the Watson Williams technique. Secondly, it may be performed by means of a pointed trocar and cannula, which was made for me by a Melbourne firm, and I have found it very satisfactory. The long handle enables one to hold the instrument as one does a pen, when directing it up between the middle turbinate and the septum to the anterior sphenoidal wall. When the anterior wall has been punctured, the trocar is withdrawn, and by means of a Higginson's syringe the lotion is passed through the cannula into the sinus and then out through the ostium. In my experience of many sphenoidal wash-outs by this method, I have found that there is no more discomfort to the patient than an ordinary antral wash-out, either in the puncturing of the anterior wall or in the actual washing through. Local anæsthesia is used. I generally carry out this procedure in my consulting rooms, with the patient seated in an ordinary examination chair. I have not as yet had any accidents, and with proper technique and knowledge of the anatomy I cannot see why there should be. The knowledge of antral lavage applies exactly to sphenoidal sinus wash-outs. Of course, in cases of obstructed nasal passages due to a grossly deviated nasal septum, it is not possible to pass the trocar and cannula in this manner. The actual site of the puncture is usually a little below the level of the ostium and lateral to the mid-line as indicated by the nasal septum. The bony wall is here thin, but inferiorly and medially it is usually much thicker. Many patients complain of local heat whilst the lotion is being syringed through the sinus. This does not appear to be related to the actual temperature of the lotion. I should be grateful if some member would offer an explanation of this phenomenon, for I have been unable to account for it. I have rarely, if ever, noted it on washing out the maxillary antrum.

TREATMENT.

Treatment resolves itself chiefly into the provision of adequate ventilation and drainage of the infected sinus, together with improving the general body resistance.

Acute Sphenoidal Sinusitis.

In acute cases the swollen tissues in the naso-pharynx, posterior choana and spheno-ethmoidal recesses need to be constricted by means of post-nasal sprays of a weak solution of cocaine hydrochloride *et cetera*. This is followed by steam inhalations. Pain and headache are relieved by aspirin mixtures. With regard to confinement to bed, one finds in practice that the patient is much more comfortable if allowed to be up and moving about in a warm room. Lying in bed is not conducive to efficient drainage of the sphenoidal sinus; but if the patient is in bed, drainage of the sinuses by posturing should be carried out at regular intervals. The temperature of the room at night should also be kept regulated so that it does not become too cold.

Chemotherapy and Physical Therapy.

Treatment by means of the sulphonamide drugs is of more use in the acute cases and in the treatment of acute complications. I have not found them of much use in chronic cases, either when used locally by introduction into the sinus or when given in tablets taken by the mouth. Penicillin nasal drops appear to help to dry up the nasal discharge in some cases. I have not had much success with using the respective solutions for washing out sinuses. I should be glad to hear the experience of members.

With regard to treatment by X rays, radiant heat and other physiotherapeutic measures, it would appear that, as in acute cases drainage is already limited, these procedures by causing further local congestion of the parts may aggravate the condition.

Treatment by deep X rays appears to help in some acute cases, but I am doubtful about its use in chronic cases.

Lavage.

With regard to lavage of the inflamed sinus, in the early stages, if it is draining adequately, it is wiser not to interfere; but later on, as the more acute signs are settling down, lavage is of distinct value in shortening the period of post-nasal discharge.

In the case of an acute empyema, drainage must be established either by lavage if possible, or by means of a sphenoidostomy.

Chronic Sphenoidal Sinusitis.

In chronic sphenoidal sinusitis again ventilation and drainage are the most important factors. Intranasal operations are designed with this purpose in view. The most important procedure is a thoroughly efficient sub-

mucous resection of the nasal septum. The resection needs to be carried far back towards the anterior walls of the sphenoidal sinuses. The usual simple anterior resection is useless, as it does not provide a clear airway across the middle turbinates to the spheno-ethmoidal recesses. In certain cases this is all that needs to be done as far as operation is concerned, for if further healing is left to Nature and sufficient time (usually a year at least) is allowed, a cure is effected.

In more advanced cases after resection of the nasal septum and removal of any polypoid tissue a sphenoidostomy needs to be performed. When this operation is performed, the turbinates are not sacrificed. All that is necessary is to press them out laterally by means of a long-bladed Killian's nasal speculum, when a good exposure of the anterior sphenoidal sinus wall is obtained for operation. It would apear that it is of the utmost importance for the future functioning of the nasal passages and sinuses that the turbinates should be intact. It is also important that the sphenoidostomy opening should not be too large.

As our object is to provide the most suitable environment for the sphenoidal sinus mucosa to recover, we must be careful to see that ventilation is not overdone, and that the natural treatment of inspired air by the nose before it reaches the sphenoidal sinus is not unduly interfered with.

The infected sinus mucosa can be treated through the sphenoidostomy opening by topical applications of various antiseptic preparations. Lavage is also carried out, but should not be overdone, as it tends to irritate the sinus mucosa if done too frequently.

In cases in which gross hyperplastic and polypoid disease of the sphenoidal sinuses is associated with a similar condition in the other nasal sinuses, it is necessary to perform one of the more radical operations designed to correct this condition, either intranasal or extranasal. But for the purpose of this paper I am confining myself as far as possible to the sphenoidal sinus itself, and therefore do not propose to enter into a discussion of these procedures.

There is only one comment that I should like to make relating to the total removal of the chronically inflamed sphenoidal sinus mucosa. This can readily be carried out in the sinuses anatomically suited; but in cases in which there are extensive pouches I have great difficulty, and the end result of the operation has been unsatisfactory.

We know that in order to clear up a gross infection of a maxillary antrum we have to remove all the mucosa completely; if pieces are left the operation is often a failure.

No post-operative treatment is carried out, apart from the use of a dry inhalation for a period of a week or ten days. Then when there is less swelling of the tissues, the sinus may be washed out.

CONCLUSION.

It would appear that an infection of the sphenoidal sinus is often an entity to itself. The posterior ethmoidal cells may be associated to a certain extent with the inflammation, but not necessarily so. The anatomical position of these cells will have a definite bearing on the condition.

SAFETY FACTORS IN COLON CANCER SURGERY.[1]

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CONSIDERABLE progress has been made during the last decade in the treatment of carcinoma of the colon, principally in the direction of the performance of primary resection rather than preliminary drainage and secondary resection. Primary resection is a safe procedure when it is performed on an adequately prepared patient whose intestinal bacterial content has been reduced by the exhibition of the appropriate "sulpha" drug.

[1] Read at a meeting of the Section of Surgery of the Australasian Medical Congress (British Medical Association), Sixth Session, Perth, August, 1948.

Right Side of the Colon.

Primary resection is the treatment of choice in carcinoma of the right half of the colon, whether obstruction is present or not. All are agreed that primary resection should be performed in non-obstructive lesions; but the surgeon is often deterred from this procedure in obstructive lesions mainly because of tradition.

When obstruction is present a preliminary short-circuit between the terminal portion of the ileum and the transverse colon has been recommended prior to resection; however, when this is done, it is not uncommon to find that so much time has elapsed that the growth has become inoperable when the second stage is attempted. In addition the patient has to suffer two intraperitoneal procedures and the surgeon is often hampered by adhesions which have resulted from the short-circuit operation.

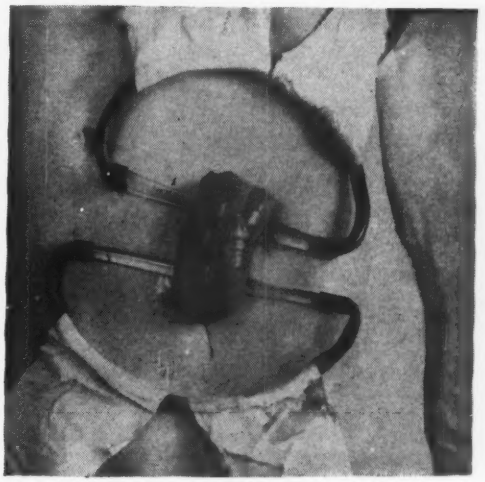

FIGURE I.

The first stage in the production of a defunctioning colostomy; a mucous membrane bridge will ultimately separate the proximal and distal openings. The colon is held outside the abdomen by two glass rods through the mesentery, placed three centimetres apart. (After Wangensteen.)

It is technically possible and surgically sound to perform a primary resection of the right half of the colon in obstructive lesions, because in practically all cases the onset of obstruction with the resulting caecal distension and right lower abdominal pain is so dramatic that operation is usually undertaken before there is any distension of the small intestine. Even should the ileum be distended the degree of distension is rarely so great as in small bowel obstruction.

CASE I.—Mr. D. McK., aged seventy-nine years, was admitted to the Royal Melbourne Hospital on October 5, 1947, complaining of severe stabbing pain in the right iliac fossa of thirty hours' duration. There was no nausea or vomiting and no history was obtainable of any previous alteration in the bowel habit. He had not lost any weight. Examination revealed a fullness in the right iliac fossa which was due to distension of the caecum; the distended caecum was palpable as a diffuse soft mass and was tender. In view of the rapid onset and the pronounced caecal distension without distension of the remainder of the colon, a diagnosis of an obstructing lesion, probably carcinoma, was made. At operation a tubular carcinoma situated about one inch distal to the ileo-caecal junction was discovered. Since the liver was free from metastases, a right hemicolectomy was performed and the cut end of the ileum was anastomosed to the transverse colon in an end-to-side manner. A drain tube was placed down to the site of the

anastomosis and removed in four days. Beyond some difficulty in micturition resulting from a benign prostatomegaly, this patient had an uneventful convalescence and has since remained well.

CASE II.—Mr. D.B., aged sixty-four years, was admitted to the Royal Melbourne Hospital on April 29, 1948, with an acute large bowel obstruction. He had suffered from central abdominal colicky pains associated with vomiting and nausea and increasing constipation for five weeks. A few days before his admission to hospital he had undergone a barium meal radiological examination, which revealed dilated small bowel loops with fluid levels and an obstruction in the ileo-caecal region with poor filling of the colon. A barium clysma was given and further radiological examination revealed a filling defect with obstruction in the ascending colon.

Clinical examination showed the patient to be an emaciated man with a pronounced degree of abdominal distension and all the other hall-marks of acute intestinal obstruction. After the stomach had been emptied by a Reyfuss tube and the lost fluid and chloride replaced by the intravenous administration of saline, a right hemicolectomy was performed, intestinal continuity being reestablished by side-to-side anastomosis between the ileum and the transverse colon. Although the ileum was considerably distended, a

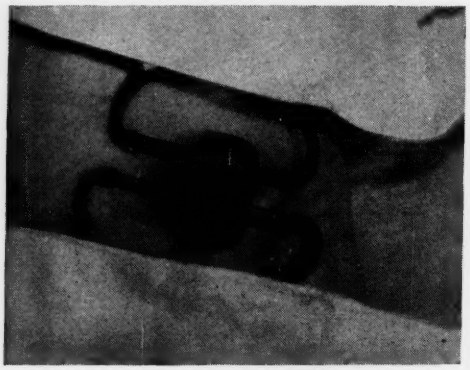

FIGURE II.

An ellipse of colon wall has been removed to allow fæcal drainage.

comparatively easy and entirely satisfactory resection was carried out through a transverse incision commencing just above the umbilicus and passing outwards into the loin. There was some post-operative infection of the outer portion of the wound, but otherwise this patient made a smooth recovery.

After resection the ileum and transverse colon may be united in an end-to-end, end-to-side or side-to-side manner. End-to-end anastomosis is the most rapid, and the cut edges of the mesenteries lie side by side and are easily joined by the application of straight artery forceps at intervals along both cut edges, the points of corresponding forceps being tied together. This is the best method of anastomosis in non-obstructive lesions or in obstructive lesions without ileal distension. In obstructive lesions with ileal distension end-to-end anastomosis carries the risk of leakage from the mesenteric angle of the cut end of the ileum. End-to-side anastomosis or, what is safer, side-to-side anastomosis, is to be preferred when ileal distension is present. There is no risk of leakage from the oversewn end of the transverse colon or of the ileum provided that the site of anastomosis is close to the oversewn ends. The disadvantage of side-to-side anastomosis is that the cut mesenteries overlap each other and are difficult to unite by the method outlined above, and it may be necessary to effect union with needle and catgut. This is a procedure fraught with some danger, because it is exceedingly easy to prick a vein with the production of hæmatoma in the mesentery. This hæmorrhage is difficult to control and the blood supply to the bowel at the anastomotic site may be jeopardized by the hæmatoma or by attempts to control the hæmorrhage.

Left Side of the Colon.

When the carcinoma lies in the left half of the colon primary resection and anastomosis is the method of choice when there is no obstruction. Irrigation of the colon through the anus, a non-residual diet and the use of the appropriate "sulpha" drugs render this procedure safe, and today it is not necessary to perform preliminary drainage proximal to the growth. However, this is a departure from past practice, and many surgeons perform a safety-valve caecostomy at the time of resection.

CASE III.—Mrs. A.W. was admitted to the Royal Melbourne Hospital on August 5, 1947, complaining of abdominal pain and diarrhœa of seven months' duration. Examination revealed a hard, fixed mass in the line of the iliac colon, and radiological examination after a barium enema showed this to be an annular carcinoma of the iliac colon. After adequate pre-operative preparation a primary resection with end-to-end anastomosis was carried out. Convalescence was uneventful and this patient remains well.

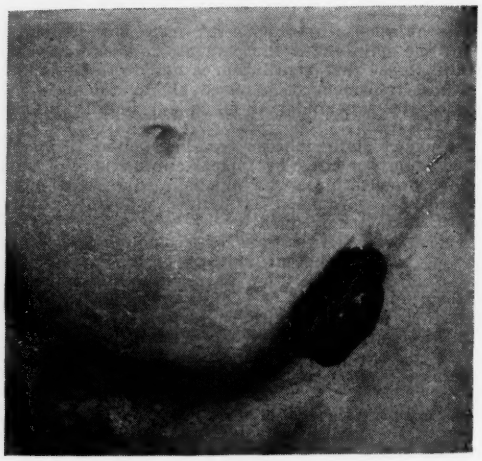

FIGURE III.

The final state. A mucous membrane bridge separates the proximal and distal openings. Closure necessitates opening the peritoneum after the extruded colon has been mobilized and the hole in the wall closed in a transverse direction.

When obstruction is present, some form of proximal decompression is necessary as a first-stage procedure. This usually takes the form of a transverse colostomy, caecostomy being reserved for very sick patients. However, with the protection now available in the second stage by the use of modern chemotherapy, caecostomy will regain its lost popularity, as the opening is easy to establish and to close, indeed it often closes spontaneously.

At the time of the preliminary operation it is customary to examine the liver and the lymph glands related to the growth and to determine the site and mobility of the growth. It is essential that the liver be palpated for metastatic deposits, for if these are present operative procedure will be limited to the performance of proximal drainage or to the establishment of a short-circuit.

The presence of hard and enlarged lymph glands related to the growth should not be regarded as a contraindication to ultimate resection. On many occasions the surgeon, after removing the growth and its related mesentery which contains hard and enlarged lymph glands, receives a report from the pathologist that the glands are free from metastatic deposits. Perhaps if serial sections of all glands were examined microscopic deposits would be found; but notwithstanding this the surgeon should not be deterred from resecting the growth, for such glands are often only the subject of inflammatory processes.

Nevertheless, despite the absence of visibly and palpable metastatic deposits in the liver, and despite a favourable report from the pathologist on the lymph glands removed, it is disconcerting to find after a successful colon resection

that the patient dies in six to twelve months from hepatic or peritoneal metastases.

The palpation of the growth to determine its exact site in the colon and its mobility is not without danger, in that careless handling of the growth may cause damage to friable or infected bowel in the neighbourhood of the growth, with subsequent leakage.

CASE IV.—Mrs. A.C. was admitted to the Royal Melbourne Hospital on May 29, 1947, complaining of abdominal pain of four days' duration and of constipation of five days' duration. A diagnosis of an obstructing lesion—probably carcinoma—of the left side of the colon was made, and this was confirmed at operation, which was limited to an abdominal exploration and the performance of a transverse colostomy. When irrigation of the left half of the colon through the colostomy opening was carried out post-operatively, the patient complained of slight lower abdominal pain. With each succeeding irrigation the pain became worse, and irrigation was stopped.

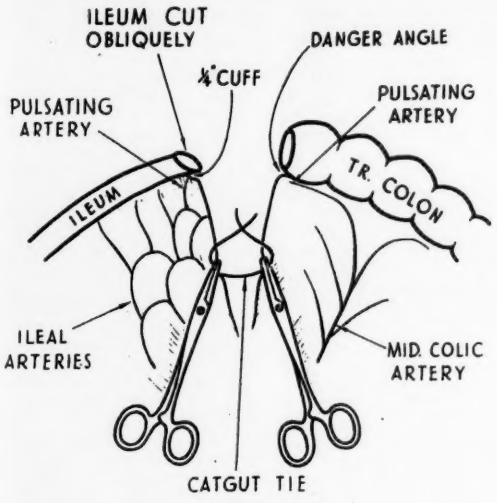

FIGURE IV.

Diagram illustrating the principle involved in performing a safe anastomosis.

After some days an attempt to resect the growth was made, but this was soon found to be impossible because of extremely extensive adhesions of the small intestine to the carcinoma almost certainly resulting from a leakage at the site of the growth. After a further period of waiting to allow the inflammatory processes to subside, another attempt at resection was made; but now the growth was inoperable because of extensive infiltration involving the bladder, coils of small intestine and the side wall of the pelvis.

The mobility of the growth determined at the time of the operation to relieve the obstruction in no way influences the assessment of operability, because fixity may be due to inflammatory changes only. Even if fixation is due to malignant infiltration, such spreading areas can and should be excised during resection unless they involve some vital structure.

Safe Anastomosis.

The safety of the anastomosis after colon resection depends on two factors: (i) accurate suturing at the anastomotic site to prevent leakage; (ii) maintenance of an adequate blood supply to the bowel at the anastomotic site.

1. Since most difficulties arise and leakage is most likely to occur at the mesenteric angle, the safest method of anastomosis is to close both cut ends and to perform a side-to-side anastomosis. This is done easily after resection of the right side of the colon, as the cut transverse colon and the cut ileum can be brought together without difficulty. In the left side of the colon this is often impossible because of the anatomical limitations to mobilization, and usually end-to-end anastomosis must be performed. The use of non-absorbable sutures for the outer layer of the anastomosis is well recognized as a safety measure to prevent leakage.

2. There is only one way to ensure that the blood supply to the anastomotic site will be adequate, and that is by direct inspection of the arterial supply to the bowel to be resected after mobilization has been completed. After the site has been determined at which the main artery to the involved segment will be ligated, such ligation should be carried out before the mesentery is divided; this is then done by cutting outwards towards the bowel. When the involved portion of the colon *plus* a segment of mesentery down to the ligated main artery has been removed, the vessels at the cut ends of the bowel are inspected to see that they are pulsating; if not, further bowel is resected until the vessels are pulsating right up to the site of section.

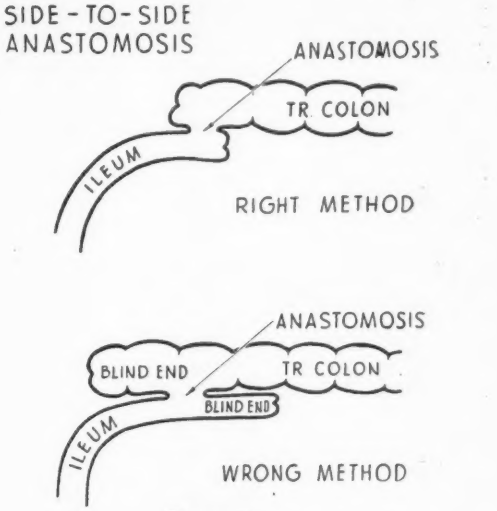

FIGURE V.

Diagram illustrating ileo-transverse colostomy; the right and the wrong method.

To ensure a safe anastomosis it is permissible to denude the cut end of the bowel of mesentery for a quarter of an inch to form a cuff for neat suturing, provided that the minute vessels can be seen pulsating right up to this cuff.

Transverse Colostomy.

There are two main methods of performing a transverse colostomy: (*a*) simple colostomy, the bowel being held onto the surface by a glass rod through the mesentery; (*b*) defunctioning colostomy, with the production of a skin bridge or a mucous membrane bridge between the proximal and distal openings.

No matter what form the colostomy takes, it is often impossible to remove all the hard fæcal masses which have collected in the colon proximal to the growth. For this reason the simple type of transverse colostomy is the better, and the apposed surfaces of the adjacent limbs of the colostomy may not be sutured together. If they are sutured together a spur is formed; this is crushed later and the colostomy is closed by an extraperitoneal operation. Even if they are not sutured, some surgeons apply an enterotome to the apposed surfaces of the adjacent limbs; but this is not without the danger of hæmorrhage or of crushing an imprisioned loop of small intestine.

When the apposed surfaces of the two limbs of the colostomy are not sutured, closure is best carried out by an intraperitoneal procedure. Intraperitoneal closure of a transverse colostomy is safe with the adoption of the following measures: (*a*) changing of gloves and instruments after closure of the bowel and before the peritoneum is opened; (*b*) washing of the closed bowel with hot saline

solution before the peritoneum is opened; (c) local parenteral and intestinal chemotherapy.

The fæcal matter which spills over from the proximal to the distal opening of a simple transverse colostomy is small in amount, is usually fluid or semi-solid, and is easily washed out of the distal part of the colon.

When it is desired to perform a defunctioning colostomy, the mucous membrane bridge variety (after Wangensteen) is the easiest opening to make and to close (*vide* Figures I to III).

No mention has been made of the modified Mikulicz procedure; this procedure is rarely indicated in carcinoma of the right half of the colon, and its use in the left half must be told elsewhere.

Chemotherapy.

It is possible to reduce the *Bacterium coli* content of the fæces by the adequate oral use of succinyl sulphathiazole or phthalyl sulphathiazole. The latter is four times as effective as the former in controlling the intestinal *Bacterium coli* content of dogs, and succinyl sulphathiazole has the disadvantage of rendering the fæces fluid.

Only 5% of the amount given of either of these drugs is absorbed from the intestine and excreted in the urine; with an adequate fluid intake and a urinary output greater than 1500 millilitres per day, there is practically no risk that crystalline deposits will form in the renal tubules. Both drugs inhibit the synthesis of vitamin *B* by bacterial activity in the bowel, and therefore the vitamin *B* complex must be given throughout treatment.

TABLE I.
Action of the Two "Sulpha" Drugs Mentioned.

Observation.	Phthalyl Sulphathiazole.	Succinyl Sulphathiazole.
Bacteria affected ..	*Bacterium coli.* *Bacillus dysenteriæ*— Flexner strain +++. Shiga strain ++. Sonne strain +. Anaerobes (?).	*Bacterium coli.* *Bacillus dysenteriæ.* Anaerobes (?).
Bacteria unaffected ..	*Streptococcus fæcalis.* *Bacillus aerogenes* and *Proteus vulgaris.*	*Streptococcus fæcalis.* *Bacillus aerogenes* and *Proteus vulgaris.*
Bacteriostatic activity ..	+++	+
Absorption	5%	5%.
Solubility in water at 37° C.	Nil.	70 milligrammes per 100 millilitres.
Toxic effects in therapeutic dose.	Nil.	Nil.
Fæcal consistency ..	Semi-solid.	Fluid.
Natural synthesis of vitamins *B* and *K*.	Diminished.	Diminished.
Dosage	Three to four grammes daily in divided doses for 10 to 18 days.	Six to ten grammes daily in divided doses for 10 to 18 days.

Because of its greater potency and because it does not render the fæces fluid, the use of phthalyl sulphatiazole is recommended. Three to four grammes per day are given in divided doses for four to seven days before operation and continued for seven to twelve days after operation. It is possible to spend the time recommended pre-operatively only in non-obstructive lesions, and at the end of this time the *Bacterium coli* content of the fæces will be reduced to the optimum of 1000 per gramme of fæces or fewer.

In carcinoma of the right side of the colon, in the presence of obstruction a right hemicolectomy is performed and administration of the drug is commenced immediately, even though the *Bacterium coli* content of the fæces will not be reduced until three or four days after the operation.

In carcinoma of the left side of the colon, in the presence of obstruction a caecostomy or a transverse colostomy will be performed. The oral use of phthalyl or succinyl sulphathiazole after the performance of a transverse colostomy is of doubtful value, as it is questionable whether the reduction of the *Bacterium coli* content of the fæces will lessen the skin irritation and infection resulting from fæcal discharge flowing over the skin. This is particularly so when the fæcal discharge remains fluid, as it does when succinyl sulphathiazole is used. There is no doubt that the skin around a colostomy opening becomes healthy most rapidly when the fæcal discharge becomes semi-solid and the colostomy discharges only once or twice per day. For this reason it is best not to use these drugs when a transverse colostomy is performed.

Since phthalyl and succinyl sulphathiazole act locally in the intestine, the *Bacterium coli* content of the colon distal to a transverse colostomy can be lessened only by irrigation with a suspension of one of these drugs. However, when a caecostomy has been performed, one of these drugs is given orally as well as being used in a suspension for colonic irrigation, both through the anus and through the caecostomy opening.

In all colon resections the site of the anastomosis is dusted with penicillin-sulphonamide powder, and penicillin injections and sulphonamides by mouth are given both before and after the operation.

Chemotherapy must not be relied upon to protect the patient from the results of indifferent surgery; the use of the "sulpha" drugs merely makes safe surgery safer.

Stomach Intubation.

It is of paramount importance to empty the stomach before a general anæsthetic is administered to a patient with intestinal obstruction. All too often an otherwise successful right colon resection or preliminary drainage operation has ended fatally because broncho-pneumonia has resulted from the aspiration of vomitus in the induction stage of the anæsthesia. This should never happen, and all patients with obstruction must be taken to the operating theatre with the stomach empty and a tube in place to enable the anæsthetist to aspirate at frequent intervals any fluid present.

The stomach may be emptied by either a Rehfuss or a Miller-Abbott tube. The latter has the advantage that, at operation, it may be manipulated through the pylorus into the duodenum, whereupon the balloon is inflated and the tube passes down the small intestine in the post-operative period. This procedure is often easy, but at other times it may be extremely difficult or impossible.

In non-obstructive lesions it is probably safer, but less necessary, to pass a tube into the stomach before operation to guard against, and to treat if it occurs, post-operative ileus.

Parenteral Fluid Therapy and Blood Transfusion.

Anæmia is the only indication for blood transfusion in the pre-operative period, and hæmorrhage the only indication in the operative and post-operative periods. In carcinoma of the right side of the colon anæmia is usually present and requires blood transfusion, but this is generally not so in left-sided growths. The loss of blood in a properly performed partial colectomy is small, and the patient should not require transfusion.

The parenteral administration of fluid is not required in the absence of obstruction before operation; but when obstruction is present intravenous saline therapy should be given to replace the lost fluid. If chlorides are absent from the urine, the intravenous saline injection is continued until they reappear, and further therapy after operation will depend on whether the patient can maintain a proper fluid balance when taking fluids orally. To obviate the collection of fluid in the tissue spaces, saline is given only in amounts necessary to prevent absence of chlorides in the urine, and is replaced at intervals by the intravenous administration of 5% glucose solution in water.

In the absence of obstruction the use of intravenous saline therapy in the post-operative period is debatable. The limitation of fluid intake by mouth rests the disturbed bowel, and this is of particular value in colon resection; fluid must then be given intravenously. This is done for the first two or three days, after which the patient is usually ready to take fluid orally and able to assimilate it.

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A CONTRIBUTION TO THE CAUSATION OF ATROPINE ALLERGY.

By E. M. TRAUTNER,
Department of Physiology, University of Melbourne.

ALLERGY against specific chemical compounds is frequently met with amongst the workers in chemical factories; it is in most cases confined to one single compound or to a group of related compounds and is usually dealt with by allotting different work to the man thus affected.

Report of a Case.

The patient in question was an athletic footballer, aged twenty-six years, fair and slender; he had the usual anamnesis of infantile diseases. Dermography was present, but he had no inclination to gastric, cardiac or nervous affections. He had no known allergy against food, dusts or other common agents and no record of atropine medication or poisoning. He had worked for eight years in a chemical factory on work of all sorts. Four years ago he was put on the processing of *Duboisia* leaf for hyoscyamine-atropine and hyoscine. After a few months he developed an increasingly aggravating affection on the exposed skin, manifesting itself in severely itching patchy eruptions in the interdigital folds and on the backs of the hands, around the neck and occasionally on the shins above the socks. The patches were of about the size of a shilling, reddish, slightly elevated, dry and covered with deep, glassy blisters of pinhead size. The blisters did not break; after a few days the patch hardened with slightly brown discoloration and subsequently either peeled off in fairly large flakes, or, if located on actively moved parts, especially in the interdigital folds, cracked and led to rather tedious and slowly healing, moist, occasionally bleeding wounds. No scars or discoloration remained after complete healing.

The affection was treated with zinc ointment and disappeared after three weeks. Within a few days after the patient had returned to work a new eruption occurred and necessitated his transfer. Since then he has been employed on varying work, including the extraction of plant material for nicotine, esculetin and other drugs; he showed no affection until he was engaged in the extraction of a bulk of *Heliotropium* species, when after four days the typical eruption recurred in full strength. His status ten days after the outbreak was as follows. The interdigital folds of both hands were reddened with seams of desquamation and in the depths of the folds were cracks exuding serous liquid. A few shilling-sized, leathery, brownish patches were present on the backs of the hands and one on the right shin. No headache and no gastric or other complications were noticed. Although the patient had been transferred to a different job on the first symptoms, the eruption took its normal course: in three to four days the outbreak appeared, in about a week the patches hardened and the itch slowly disappeared, the final healing depending on the presence or absence of secondary injury to the affected parts of the skin. It may be noted that the patient never showed symptoms of acute or chronic atropine-hyoscine poisoning, dryness of the throat *et cetera*, except the occasional slight mydriasis which is difficult to avoid during handling of the dried, ground plant material; and that in the processing of the *Heliotropium* he was engaged only in loading the percolators with the dry plant material and starting alcoholic extraction.

Discussion.

The case is interesting because the alkaloids of *Heliotropium* and related plants belong to a group entirely different from the tropine-bases, and their toxicological action is different from the well-defined action of atropine or hyoscine. They are stated to cause hæmorrhages in various organs, but always in the liver, and they lead in the sheep after several months or in the second year to cirrhosis of the liver. The plant contains very little (only about 0·05%) of alkaloids, and the damage develops slowly. There is, however, a chemical analogy between the two groups of alkaloids; both are tertiary bases containing one nitrogen atom in alicyclic rings and at least one esterified hydroxyl group. The ring system of the tropine bases is shown in Figure I (*a*), the asterisk marking the carbon atom on which esterification takes place; the crosses mark the two carbon atoms where there is an oxygen bridge in hyoscine or one or two non-esterified hydroxyl groups in the by-alkaloids. Figure I (*b*) shows the heliotridane skeleton, which in the alkaloids contains one double bond and two hydroxyl groups, on two of the positions tentatively marked with asterisks. The exact position of these substitutions is not known, and one or both of these hydroxyl groups are esterified. The thick lines in the tropane ring follow the steric constellation: nitrogen–three carbon atoms–linking ester. In the heliotridane ring one of the possible configurations is outlined; all the others, however, show exactly the same sequence of atoms between nitrogen and the linking ester. This section is identical in the two groups of alkaloids.

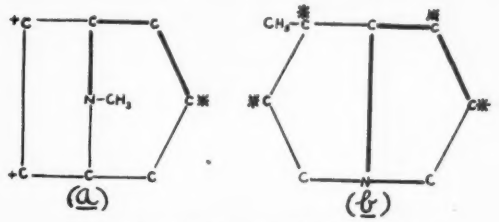

FIGURE I. (*a*) Tropane, (*b*) heliotridane.

The toxicological action of the atropine-hyoscine group is based on the tropine skeleton and its esterification with the specific aromatic acid, tropic acid; it is suggested that the toxic action of the *Heliotropium* and related alkaloids is based on the heliotridane nucleus and its esterification with specific aliphatic acids of varying composition, the pharmaceutical action being entirely different. Only the steric relation of nitrogen to the linking ester is identical.

Usually allergies in chemical work take some time to develop and then are aggravated. The reaction to *Heliotropium* was immediate and in all symptoms identical to the reaction to atropine-hyoscine. It is therefore considered that the effect is not due to two separate allergies caused by different agents, but that it is caused by the identical grouping of the tertiary nitrogen with respect to the linking ester. The remaining molecules determine the pharmacological actions, but are of minor or no importance in the allergic action. In the allergic effect the two alkaloids can replace each other.

THE EFFECT OF LIGATION OF THE PANCREATIC DUCTS UPON THE ACTION OF ALLOXAN IN THE DOG.

By DAVID MONK ADAMS, M.B., M.Sc.,
From the Department of Physiology, University of Sydney.[1]

IT is now well established that the injection of an appropriate dose of alloxan into an animal is followed by a characteristic triphasic response in the blood sugar level and a selective necrosis of the islets of Langerhans, which results in permanent diabetes. Such a response is illustrated in the control animals of this experiment.

Walpole and Innes(1) have reported on the effect of alloxan administration in rabbits at various periods after ligation of the main pancreatic duct. They claim that, when sufficient time is allowed to elapse after the operation

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TABLE I.

Dog Number.	Duct Ligation.			Dose.[1]	Blood Sugar Values. (Milligrammes per 100 Millilitres) at Time in Hours after Alloxan Injection.						Glycosuria.
	Day Since.	Weight in Kilograms.			0	2	4	6	24	48	
		Before.	After.								
1	67	6·79	4·55	100	117	128	119	115	113	111	No.
2	42	10·86	9·54	75	95	105	110	107	98	116	No.
Control											
1	—	5·30	—	100	98	421	104	32	237	579	Yes.
3	39	9·10	7·63	75	102	119	112	93	103	95	No.
4	96	8·76	6·22	100	153	188	157	150	147	Died.	No. (Urine in bladder.)
Control											
2	—	7·61	—	75	101	307	92	40	213	461	Yes.

[1] Dose of alloxan in milligrammes per kilogram of body weight.

to permit the acinar tissue to degenerate, the subsequent administration of alloxan produces comparatively small blood sugar changes, little or no change in the histology of the surviving islet cells, and no diabetes. The purpose of this communication is to confirm their findings, the experimental animal in this case being the dog.

Experimental Procedure.

The dogs were all adult males; their weights before and after operation and the length of time between operation and injection are recorded in Table I. The operation was performed under "Dial" anæsthesia, the agent being injected intraperitoneally.

The pancreatic ducts were cut between silk ligatures, the pancreatic end of each duct was turned back upon itself and sutured to the pancreas, and omentum was drawn over and sutured between the head of the pancreas and the second part of the duodenum. This procedure was adopted to prevent the possibility of recanalization of either duct.

The alloxan monohydrate used had been freshly prepared by Mr. G. K. Hughes, of the Department of Organic Chemistry, University of Sydney. It was kept cold and dry, and solutions were freshly prepared within half an hour of each injection. The solution used was a 5% solution in sterile water; it was injected into a leg vein, and the duration of injection was timed to last one minute. The animals were fasted for twelve hours, a blood sample for fasting blood sugar estimation was then taken, and two minutes later the alloxan was administered. All blood samples were taken in duplicate, 0·1 millilitre of blood being obtained from a marginal ear vein and examined for sugar content by means of the method of Hagedorn and Jensen.

Forty-eight hours after the injection of alloxan the dogs were anæsthetized with "Dial" and killed by the intravenous injection of several hundred millilitres of formalin, which was allowed to replace the circulating blood. The pancreas was fixed for three to four months in 10% formol-saline solution and imbedded in paraffin. Sections were stained with hæmatoxylin-eosin.

Control animals were not operated upon, but were fed identical diets. Both control and duct-ligated animals received the same subcutaneous injection of 20% glucose solution, commencing six hours after the alloxan administration. All urine was tested for sugar by Benedict's test, the urine having been passed forty-four to forty-eight hours after the alloxan injection.

In the two control animals the histological picture of the pancreas was that of coagulative necrosis, as is usually seen following an appropriate dose of alloxan. The islet cells were shrunken and fused into a mass with a few apparently normal cells seen at the periphery.

In all the duct-ligated animals the pancreas was smaller and harder than in the normal. Microscopically the acinar tissue had undergone extreme atrophy, and much fibrotic tissue was present in all cases. In those dogs whose ducts had been ligated for sixty-seven and ninety-six days, the fibrosis was much more extensive, while the gland was smaller and firmer macroscopically. In all the duct-ligated animals the islet tissue appeared normal.

Discussion.

It can be seen from the table that the duct-ligated animals showed very slight blood sugar responses to the injection of diabetogenic doses of alloxan. None of them developed diabetes, however, nor did their islets show signs of degeneration. These three findings are in marked contrast to the usual response to alloxan, as is demonstrated in the control animals.

Walpole and Innes have suggested that the lack of response in the duct-ligated animals may be due to the fact that (*a*) the acinar tissue of the pancreas is in some way involved in the action of the alloxan upon the islets, or (*b*) the extensive fibrosis of the pancreas prevents the access of the alloxan (which is very rapidly destroyed) to the islets in sufficient quantities to cause degeneration. Both animals one and four, whose ducts had been ligated for sixty-seven and ninety-four days, had high fasting blood sugar levels, suggesting that the islets were not fully functioning, possibly because of diminished blood supply. Further experiments are being conducted, producing sclerosis in only half of the pancreas; these should demonstrate whether the sparing effect of duct-ligation is due to diminished vascular supply, to absence of acinar tissue, or to some other factor.

Summary.

1. By means of ligating the pancreatic ducts of dogs and subsequently injecting alloxan it was found that diabetes was not produced.

2. This result confirms the findings of Walpole and Innes in the rabbit.

Acknowledgements.

I wish to thank Dr. Rosina Wells and Mr. John Hanneran for assistance in the operations.

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Reports of Cases.

A CASE OF APLASTIC ANÆMIA DUE TO GOLD THERAPY TREATED WITH BAL.

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GOLD THERAPY has been used widely in the treatment of certain skin diseases, of tuberculosis, and particularly of rheumatoid arthritis. Unfortunately toxic effects of varying degrees of severity have limited the use of chrysotherapy in rheumatoid arthritis. The most common reactions are generalized pruritus, urticaria, stomatitis, gastro-enteritis,

purpura, agranulocytosis, aplastic anæmia, exfoliative dermatitis and nephritis.

Hartfall *et alii*[1] reported a 41·9% incidence of toxic reactions among 900 cases. Of these reactions 6% were severe, with seven deaths—three from hæmorrhagic purpura, one from agranulocytosis, two from liver necrosis and one from exfoliative dermatitis. There were adverse hæmatological reactions in ten cases in all. In 1942 Cecil *et alii*[2] reported on 245 patients treated with gold. Of these, 105 had toxic manifestations (42%); in four cases the complications were hæmatological and included three cases of hæmorrhagic purpura and one of agranulocytosis. In 1947 Cohen *et alii*[3] reported toxic reactions in 20% to 56% of 750 courses of gold injections.

Hæmatological manifestations of toxicity, though relatively rare, are among the most serious. Of these, thrombocytopenia is the most common, with agranulocytosis next in frequency and aplastic anæmia the rarest and most serious.

Dameshek[4] reviewed the literature in 1934 and reported six cases of aplastic anæmia, one case of agranulocytosis, and one case of *purpura hæmorrhagica*, and added a case.

Wintrobe *et alii*[5] in 1939 reported a further case of aplastic anæmia and reviewed the literature, making the total of hæmatopoietic reactions due to gold as follows: thirteen cases of aplastic anæmia, ten of agranulocytosis, seven of *purpura hæmorrhagica*.

Lockie *et alii*[6] in 1947 reported two further cases, one of thrombocytopenia and one of agranulocytosis.

Fitzpatrick and Schwartz[7] in 1948 reviewed the literature and reported two additional cases of aplastic anæmia, making a total of 20 cases of aplastic anæmia following gold therapy with four recoveries.

In the following case of aplastic anæmia the patient first began to show symptoms ten months after the beginning of chrysotherapy.

In view of the improvement, particularly in the granulocytic reaction following the exhibition of BAL, I feel that the recording of this case would be of interest, especially since previously poor therapeutic results had been achieved in similar conditions.

Clinical Record.

V.M., a female, married, aged fifty-three years, was first examined on March 4, 1948, complaining of epistaxis. The nose was packed with adrenaline gauze, and after two hours, when the hæmorrhage had stopped, she was allowed to go home. Her systolic blood pressure was 110 millimetres of mercury and her diastolic blood pressure 70 millimetres. She was admitted to hospital on March 6 with recurrence of epistaxis from the right nostril. Her nose had to be packed twice before the hæmorrhage ceased. The bleeding point was not seen and her blood pressure was 110 millimetres of mercury, systolic, and 70 millimetres, diastolic. She gave a history of an epistaxis which had begun suddenly several days prior to her first visit to hospital and stopped after several hours. She had not complained of any other symptoms and she felt well.

The patient has for many years been suffering from rheumatoid arthritis involving her knees, her wrists and the small joints of her fingers. In July, 1947, she began a course of weekly injections of "Myocrisin" (0·05 gramme per dose), lasting for twelve weeks. Two weeks after the final injection she complained of a scaly, irritable rash on both forearms, which cleared up with the application of zinc cream. She felt well and the pains in her joints were less severe. She has never menstruated except for one slight show of blood as a young girl, which lasted for only one day. She is married, has no children and has had no miscarriages. Her family history was irrelevant.

Physical examination revealed the patient to be a plump woman of her stated age, in no apparent distress. The skin of the face was smooth, the eyebrows were thinning from the lateral margins, the skin of the trunk was smooth and soft, and there was no abnormal pigmentation of the skin. There was a complete absence of pubic, axillary and superficial hair. The breasts appeared to be composed of fatty tissue with faint areolæ at their summit and a complete absence of nipples. The tongue was smooth and there was no atrophy of the papillæ. No glands were palpable in the axillæ or in the groins. The spleen and liver were not palpable. No abnormality pertaining to the other systems was found. Vaginal examination revealed a narrow introitus, a hard cervix and an infantile uterus; ovaries and Fallopian tubes were not palpable. The patient experienced much discomfort from this examination.

On March 10 the patient's temperature rose to 103° F. and she developed a generalized morbilliform type of rash. Her pulse rate was 90 per minute. A blood count on this day showed that the leucocytes numbered 1200 per cubic millimetre; 34% were polymorphonuclear cells, 62% lymphocytes, 2% eosinophile cells and 2% monocytes; no primitive cells were seen.

On March 11 she complained of headache and general malaise and developed petechial spots over the whole of her trunk, lower limbs and arms, and on the palate and gum margin where the dentures made contact. The tourniquet test produced a positive result. Her blood pressure was 100 millimetres of mercury, systolic, and 70 millimetres, diastolic. Her pulse rate was 90 per minute and her temperature 103° F. A blood count gave the following information. The erythrocytes numbered 2,420,000 per cubic millimetre, the hæmoglobin value was 62% (14·5 grammes *per centum* = 100%), and the colour index was 1·29. The leucocytes numbered 1200 per cubic millimetre, 26% being neutrophile cells, 72% lymphocytes and 2% eosinophile cells. The coagulation time was two minutes. The platelets numbered 3500 per cubic millimetre. The bleeding time was one hour. Of the erythrocytes, 1·2% were reticulocytes; anisocytosis was present and no primitive cells were seen.

On March 12 the purpuric rash was more pronounced and dark blue and purple in areas. The diagnosis of aplastic anæmia presumably due to gold therapy was made.

On March 14 a blood transfusion was commenced, and on March 14, 15 and 16 the patient received a total of three litres of blood.

On March 18 her blood count and hæmoglobin value had improved; but the platelet count was still very low (Table I).

Treatment consisted of the administration of 25,000 units of penicillin every three hours, vitamin *K* injections every four hours, and of the administration of vitamin *C* (150 milligrammes daily), vitamin B_1, vitamin *B* complex, folic acid (five milligrammes three times a day), ferrous sulphate (18 grains per day), liver extract and brewer's yeast. The site of the needle puncture oozed blood and the bleeding time was prolonged to hours.

Urine examination on March 19 revealed the presence of 20 to 25 erythrocytes per high-power field; albumin was present and no casts were seen.

On March 23 and 24 the patient received two further blood transfusions of 600 millilitres of blood each. She had frequent rigors following each transfusion (temperature 105° F.). She had several severe epistaxes and there was increasing difficulty in stopping them.

On March 24 she complained of earache and of a brownish discharge from the right ear. Examination revealed œdema of the external auditory meatus, with hæmatomata behind the drums of both ears and small petechiæ on each drum.

"Pentnucleotide" therapy was commenced on April 7 because of the low leucocyte count and the low polymorphonuclear cell percentage (4%—Table I). The dose given was 10 millilitres intramuscularly per day, and on April 9 the number of leucocytes had increased by 200 per cubic millimetre, mainly in the polymorphonuclear cells. Because the patient had a severe reaction following each injection, consisting of a rigor (temperature 102° F.), restlessness and generalized malaise, the total dose was divided into four equal parts. The next leucocyte count on April 12 revealed a further drop, mainly in the polymorphonuclear cells. Although it is not possible to draw any definite conclusion from this isolated instance, none the less it strongly suggests that for "Pentnucleotide" to be effective it must be given in full doses.

TABLE I.
Hæmatological Data.

Date.	Hæmoglobin Value. (100% = 14·5 G.)	Erythrocytes per Cubic Millimetre.	Leucocytes per Cubic Millimetre.	Neutrophile Cells. (Per Centum.)	Juvenile Cells. (Per Centum.)	Eosinophile Cells. (Per Centum.)	Lymphocytes. (Per Centum.)	Monocytes. (Per Centum.)	Colour Index.	Platelets per Cubic Millimetre.	Reticulocytes. (Per Centum.)	Coagulation Time. (Minutes.)	Bleeding Time. (Minutes.)	Remarks.
10/3/48	—	—	1,200	34		2	62	2	—	—	—			
12/3/48	62% (9 G.)	2,420,000	1,200	26		2	72	—	1·29	3,500	1·2			Blood transfusion, 3 litres.
18/3/48	82% (11·9 G.)	3,510,000	1,200						1·17	2,150		2		
23/3/48	—	—	—	—		3	—	—	—	—	—	6	12	
5/4/48	64% (9·3 G.)	2,760,000	2,300	4			92	1	1·18	—				"Pentnucleotide", 10 millilitres.
9/4/48	56% (8·1 G.)	—	2,500	12			85	3	—					
12/4/48	52% (7·5 G.)	2,470,000	2,100	3			94	3	1·08					
15/4/48	88% (12·8 G.)	4,590,000	3,000	33	0·5		65	2	0·88					Blood transfusion, 2 litres.
20/4/48	82% (11·9 G.)	3,480,000	2,700	18	0·5		70	12	1·17	1,200				
27/4/48	62% (9·0 G.)	2,400,000	2,470,000	8	1·0		88	4	1·3					
29/4/48	60% (8·7 G.)	2,380,000	1,800	8		2	88	2	1·3	—				BAL therapy commenced (1).
3/5/48	46% (6·7 G.)	2,010,000	2,200	30	3·0		70		1·15	Few				
7/5/48	30% (4·3 G.)	—	1,800	56	6·0		34	10	—	—				
13/5/48	92% (13·3 G.)	4,660,000	1,300	32	15·20		46	22	1·0	40,000				Blood transfusion, 3·2 litres.
17/5/48	82% (11·9 G.)	—	3,400	22	—		69	9	—	—				
20/5/48	92% (13·3 G.)	5,090,000	4,100	26	3·0	1	68	5	0·9	Few				
22/5/48	90% (13·1 G.)	4,000,000	3,200	15			77	8	1·15					
24/5/48	86% (12·5 G.)	3,720,000	2,900	21			63	16	0·9					BAL therapy commenced (2).
4/6/48	38% (5·5 G.)	2,260,000	2,700	22		2	62	14	1·28	—				
10/6/48	76% (11·0 G.)	3,010,000	1,900	—			—	2	1·26					
15/6/48	74% (10·7 G.)	3,560,000	3,800	20		11	55	13	1·05	Few				Blood transfusion, 2 litres.
18/6/48	66% (9·6 G.)	2,990,000	3,300	—			—	—	1·0	—				Eosinophilia.
21/6/48	58% (8·4 G.)	2,220,000	3,000						1·0					
25/6/48	56% (8·1 G.)	2,410,000	4,200						1·17					
29/6/48	48% (7·0 G.)	2,410,000	3,000						1·0					
7/7/48	54% (7·8 G.)	2,230,000	2,200						1·2					
9/7/48	52% (7·5 G.)	1,900,000	3,200	18		3	71	8	1·3					
13/7/48	52% (7·5 G.)	2,690,000	2,200	38			58	4	1·0					
19/7/48	62% (9·0 G.)	2,760,000	2,600	—			—	—	1·1					
20/7/48	58% (8·4 G.)	2,320,000	2,600						1·26					
26/7/48	60% (8·7 G.)	2,720,000	3,800	23			70	7	1·11	Few				
28/7/48	66% (9·6 G.)	2,750,000	4,200	40			54	6	1·22	10,000				
11/8/48	74% (10·7 G.)	3,040,000	4,500	33			58	9	1·23	12,000	5·2			
23/8/48	82% (11·9 G.)	3,620,000	4,400	41			50	9	1·14	15,000				

Sternal marrow puncture was performed on April 24, and examination of the smears by the Department of Public Health Laboratory and by another independent pathologist confirmed the diagnosis of aplastic anæmia (Table II). Though the films suggested dilution by peripheral blood, there was considerable depression of marrow activity affecting both the red and white cells, with a relative increase in the percentage of lymphocytes.

In spite of the treatment described, the patient still had progressive anæmia, leucopenia and thrombocytopenia, and a further blood transfusion was given on April 12 (two litres of blood). After this transfusion she had a rigor and a temperature of 104·8° F., with pronounced hæmaturia and albuminuria.

Quantitative analysis of the urine for gold, carried out by the Department of Public Health chemical laboratory on April 21, showed gold to be present in the quantity of 0·026 milligramme per litre.

As gold was still being excreted, it was decided to treat the patient with BAL (British anti-Lewisite) in the hope that it might hasten the excretion of gold and so perhaps allow the marrow to regenerate.

BAL treatment was begun on April 24 with an intramuscular injection of a dose of two millilitres in 5% solution in arachis oil containing benzyl benzoate (10%). The course consisted of four intramuscular injections at intervals of four hours during the first twenty-four hours; then one ampoule was given twice a day for the next three days and one ampoule once a day for the next two days. She had little reaction from these injections and showed no toxic symptoms from the BAL.

On May 6, the day after the BAL course was completed, her urine still contained gold in quantities of 0·02 milligramme per litre (Table III).

The blood picture during the course of BAL is interesting, as there was an increase in the percentage of polymorphonuclear cells (from 8% to 56%), suggesting a regeneration in the granulocyte series (Table I). However, the hæmoglobin value and the number of erythrocytes continued to fall, and on May 7 her hæmoglobin value was 30% (4·3 grammes *per centum*); she was given a further transfusion of 3·2 litres of fresh blood on May 10.

On May 13 her hæmoglobin value was 92%, the erythrocytes numbered 4,660,000 per cubic millimetre; the leucocytes numbered 1300 per cubic millimetre, 32% being neutrophile cells (juveniles 15% to 20%), 46% lymphocytes and 22% monocytes; platelets numbered 40,000 per cubic millimetre.

After the excellent response of the granulocytes to the first course of BAL a second course was begun on May 24, in the hope that a similar effect would be obtained in the erythrocyte series; however, no regeneration of erythrocytes was observed and a further two litres of fresh blood were given on June 10.

Further examination of her urine showed that on June 1 less than 0·005 milligramme of gold per litre of urine was excreted in twenty-four hours. Thus all the gold which had been held in the tissues had been excreted by June 1, roughly twelve months after the institution of gold therapy.

On July 21 a further bone marrow puncture was performed and examination of smears by the laboratory of the Department of Public Health revealed a normoblastic reaction with a pronounced increase in the normoblasts (53%).

The blood picture on July 28 was as follows: the erythrocytes numbered 2,750,000 per cubic millimetre, the hæmoglobin value was 66%, and the colour index was 1·22; the leucocytes numbered 4200 per cubic millimetre, 40% being neutrophile cells, 58% lymphocytes and 6% monocytes; platelets numbered 10,000 per cubic millimetre, and 5·2% of the red cells were reticulocytes.

She was discharged from hospital on July 29, well physically and clinically. On August 11 her blood picture

TABLE II.
Differential Count of Bone Marrow Smears.

Cells.	Normal.[1] (*Per Centum.*)	Present Case.	
		24/3/48.	20/7/48.
Granulopoietic series :			
Premyelocytes	0·5 to 5·0	1·0	1·0
Myeloblasts	0 to 2·5	1·0	4·0
Differentiated myelocytes :			
Neutrophile cells	2·0 to 8·0	3·0	10·0
Eosinophile cells	0 to 1·0	1·0	—
Basophile cells	—	—	—
Metamyelocytes :			
Neutrophile cells	2·5 to 12·0	—	—
Eosinophile cells	0 to 2·5	—	—
Basophile cells	—	—	—
Polymorphonuclear leucocytes :			
Neutrophile cells	20·0 to 50·0	2·0	15·0
Eosinophile cells	0 to 4·0	2·0	—
Basophile cells	0 to 1·0	—	—
Lymphocytes	5·0 to 20·0	80·0	17·0
Monocytes	0 to 5·0	—	—
Plasma cells	0 to 1·0	—	—
Megakaryocytes	0·03 to 3·0	—	—
Erythropoietic series :			
Normoblasts	7·0 to 19·0	11·0	53·0
Erythroblasts	2·0 to 7·0	—	—
Megaloblasts	0 to 4·0	—	—
Reticulocytes	5·0	—	—

[1] From " Disorders of the Blood ", by L. E. H. Whitby and C. J. C. Britton.

was as follows: the erythrocytes numbered 3,440,000 per cubic millimetre, the hæmoglobin value was 74%, the colour index was 1·23, and platelets numbered 12,000 per cubic millimetre; the leucocytes numbered 4500 per cubic millimetre.

Although high hopes of a cure were held out, the patient had a relapse and was readmitted to hospital on September 20, with further epistaxis and a hæmoglobin value of 24%. She had further blood transfusions of four litres of blood on September 24, when her hæmoglobin value was 94%.

TABLE III.
Gold Content in Twenty-four Hours Specimen of Urine.

Date.	Milligrammes of Gold per Litre of Urine.
21/4/48	0·026
6/5/48	0·02
24/5/48	Less than 0·005
1/6/48	Less than 0·005

During the patient's stay in hospital she received 14,000,000 units of penicillin and suffered little discomfort from the injections, except for an abscess on the thigh, which responded to the usual treatment. She had no toxic reactions from the BAL injections.

Discussion.

The mechanism of the production of toxic symptoms due to gold, particularly the hæmatological manifestations, is not fully known, and animal experimentation has failed to reproduce these toxic symptoms (Wintrobe *et alii*[5]). Clinical evidence favours individual sensitivity, since the severity of toxic symptoms has little relationship to the amount of drug used. Bomford and Rhoads,[6] in their article on "Refractory Anæmia", state that persons exposed to a potentially toxic substance exhibit a varying susceptibility, that individuals may become sensitized to a drug, showing symptoms after taking subsequent doses, and also that symptoms may not immediately follow the taking of a toxic substance, but may be considerably delayed.

In the case under discussion the patient first showed mild dermatitis two weeks after cessation of gold therapy, and the severe hæmatological reaction occurred almost seven months after chrysotherapy was completed.

It is known that gold can be retained in the tissues for long periods of time, exerting its beneficial and/or toxic effects. In this case gold was still being excreted in the urine eight months after the cessation of chrysotherapy, when the patient first exhibited signs of hæmatological disturbance. Since it was not until June 1 that the last of the gold was excreted in the case under discussion, gold was held in the tissues for approximately twelve months.

Bomford and Rhoads[6] in their article pointed out an interesting association of endocrine disorders with the refractory anæmias. In 66 cases of refractory anæmia, four patients had a history of an endocrine disorder, five patients reported an association of an endocrine disorder in near relations, four women first noticed their symptoms at or very near their menopause, two women noticed that their symptoms were more severe at or shortly before the time of menstruation. The authors suggest that in the light of their findings further investigation is desirable in order to determine whether these endocrine disorders are a contributory factor in the onset and course of the refractory anæmias. It is interesting to note that the patient under discussion has a history of hyposexuality with complete absence of secondary sex characteristics.

Until recently toxic reactions due to heavy metals have been largely treated symptomatically, and only with the discovery of BAL (British anti-Lewisite, 2,3-dimercaptopropanol) as an antidote to Lewisite gas and its effective application in arsenical poisoning has new hope developed for the treatment of toxic reactions due to gold.

Lately several reports dealing with BAL and the treatment of gold toxicity have been published. Lockie *et alii*[4] treated two patients with hæmatological reactions due to gold therapy and complete recovery resulted. Fitzpatrick and Schwartz[7] treated one patient with BAL, and because they used it at a very late stage no importance could be attached to the end result. Other authors have had promising results in treating forms of dermatitis and other toxic reactions due to gold. However, all authors are unanimous in their opinion that in order to be effective BAL therapy must be instituted soon after the toxic symptoms appear, otherwise the toxic changes become irreversible.

In the case under discussion BAL therapy was commenced nine months after gold therapy had been completed. The delay was mainly due to the fact that the patient did not present herself for treatment until eight months after the cessation of gold injections, and also due to the difficulty in obtaining supplies of BAL. The fact that gold was still being excreted in the urine prompted the trial of BAL, in the hope that it would accelerate the excretion of gold from the body and so allow the bone marrow to regenerate.

Although little change in the blood picture followed the first course of BAL, the neutrophile cell percentage began to increase from that date (Table I). The only conclusion that could be drawn at that stage was that BAL had caused a stimulation of the granulocyte series. This effect was so heartening that a second course of BAL was instituted; but once again there was little response from the red cells.

However, once all the gold had been excreted from the body, and after her last blood transfusion on June 10, the patient's hæmoglobin value remained stable and even began to rise. Examination of bone marrow smears on July 21 confirmed the suspicion that the marrow was regenerating

(Table II). But on September 20 the patient's hæmoglobin value once again fell to 24%, which necessitated further blood transfusions. Although BAL did not produce a cure in the present case, it is significant to note that the neutrophile cell percentage remained at the higher level, and I feel sure that if BAL therapy had been instituted at an early stage a more hopeful result would have been obtained.

It appears from the case described and from cases reported by other authors that BAL is of value in intoxications due to heavy metals, and to exert its maximum effect it must be used early after the onset of toxic symptoms.

Owing to the fact that BAL is a specific antidote against poisoning due to heavy metals, including gold, one may expect the more liberal reinstitution of chrysotherapy in the near future. The availability of BAL may diminish the alarm usually associated with toxic reactions, and further research into the mode of action of gold in rheumatoid arthritis and into the mechanism of production of toxic symptoms may thus result.

Summary.

1. A case of aplastic anæmia due to gold therapy has been presented. Symptoms first appeared eight months after the last injection, and gold was shown to be present in the tissues twelve months after therapy was begun.

2. Association of an endocrine disorder (hyposexuality) with the aplastic anæmia is shown. This disturbance may have had some influence on the patient's susceptibility to hæmotological reactions following the exhibition of a heavy metal. Bomford and Rhoads[6] pointed out this same association in their series of cases of refractory anæmia due to various factors.

3. The effect of BAL on aplastic anæmia due to gold toxicity has been discussed. It appears from the case history that BAL was responsible for (*a*) increased excretion of the residual gold held in the tissues, (*b*) regeneration of the granulocytic series.

It appears that BAL is an effective drug for the treatment of hæmatological and other toxic manifestations due to heavy metals, if administered at an early stage.

Acknowledgements.

I wish to acknowledge my indebtedness to Dr. C. Luscombe for granting permission to publish this case, to Dr. F. Hales Wilson for his valuable advice, and to Dr. L. R. Rail and Mr. A. Chapple, of the pathology department, for their help and interest in the progress of the patient.

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AN UNUSUAL CONGENITAL CARDIAC ANOMALY.

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J.D., a male subject, aged eight days, was admitted to the children's ward of the Alfred Hospital on November 7, 1947, with a congenital deficiency of the abdominal wall.

The deficiency was in the region of the umbilicus, circular in outline and about two inches in diameter. It was surrounded by reddened skin to a depth of a quarter of an inch, and was covered by dry, greyish-yellow tissue containing dried blood clot. There was a semilunar area with prominent veins over the superior aspect of the deficiency. Herniation of the abdominal contents covered an area of approximately three inches in diameter. Surgical repair was performed successfully, but the baby died soon after the operation.

A post-mortem examination was carried out and an unusual congenital cardiac anomaly was revealed. The right atrium, which received the superior and inferior *venæ cavæ* in the usual way, was dilated and communicated with the left atrium by a patent *foramen ovale*. It led by a normal tricuspid valve into a large right ventricle.

The aorta, which was about twice the diameter of the pulmonary artery, arose from this ventricle in the normal position of the pulmonary artery. The pulmonary artery also arose from the right ventricle to the left of the aorta, the pulmonary and aortic valves being separated by a thick band of muscle.

Pulmonary and aortic valves appeared normal. Between the tricuspid valve and aortic valves there was a large interventricular foramen; this was the only outlet for the small left ventricle, which received blood from the lungs via the left atrium and mitral valve in the usual way. The remainder of the aorta was normal and the *ductus arteriosus* was closed.

Reviews.

MEDICAL TREATMENT.

THE fifth edition of "A Textbook of Medical Treatment", by Dunlop, Davidson and McNee, is to hand.[1] The preface draws attention to three new chapters on antihistamine drugs, treatment of dehydration and hypochlorræmia and the care of old people. In the chapter on the antihistamine drugs the author, unlike many writers on allergy, makes no extravagant claims and expresses the disappointment experienced by most practitioners following their use in asthma. Their value in the treatment of the skin allergies is recorded.

The chapter on dehydration and hypochlorræmia is excellently set out and should be made a routine study for all resident medical officers. This might prevent much of the trouble from over-enthusiastic saline medication, and a more rational approach to these problems might be brought about. The writer acknowledges his debt to Marriott's Croonian Lectures, but it is good to see these principles set out in a standard text-book. It is interesting to note the attention paid here and elsewhere to a simple test like Fantu's test for urinary chlorides, which, though advocated twenty-five years ago, has had to await recent years for acceptance.

The section on pulmonary tuberculosis was favourably commented upon in our review of the fourth edition and its general high standard remains. However, one is surprised to find but a paragraph on the use of streptomycin with the comment that "at the time of writing streptomycin is not available for private use". Even at the end of 1948 there was sufficient evidence to justify some comment. By contrast

[1] "Textbook of Medical Treatment", by various authors, edited by D. M. Dunlop, B.A. (Oxon.), M.D., F.R.C.P. (Edinburgh), F.R.C.P. (London), L. S. P. Davidson, B.A. (Cambridge), M.D., F.R.C.P. (Edinburgh), F.R.C.P. (London), M.D. (Oslo), and J. W. McNee, D.S.O., D.Sc., M.D. (Glasgow), F.R.C.P. (Edinburgh), F.R.C.P. (London); Fifth Edition; 1949. Edinburgh: E. and S. Livingstone, Limited. 9" x 6", pp. 1020, with 40 illustrations. Price: 35s.

there are nearly two pages on tuberculin treatment. Whatever may be the final assessment of streptomycin, there was no doubt even a year ago of its efficacy, for example in laryngeal tuberculosis, of its usefulness in conjunction with surgery in tuberculosis, and of the risk of and necessary precaution against the occurrence of bacterial resistance following its use.

We note that in the chapter on the treatment of diabetic coma the authors again stress the necessity for large initial insulin dosage. On this occasion we do not have to quarrel with them about the early intravenous use of glucose as a "cover" for insulin. They now state that "it is unnecessary and even undesirable to 'cover' these initial doses [of insulin] with glucose, which used to be thought such an essential part of the treatment".

There is a well presented chapter on diseases of the thyreoid gland, including a valuable résumé of the thiouracil therapy of thyreotoxicosis.

The section on diseases of the blood is one that we have come to expect from these distinguished writers in the field of hæmatology. Is it then likely to be accepted as carping criticism if we say that a book so widely distributed should refer to hæmoglobin values in grammes rather than the percentage "Hb. value"? We refer them to their plea in the preface for the metric system in dosage.

There is a balanced summing up of the indications for surgery in the treatment of peptic ulcer and its complications. Apparently the Edinburgh school has never heard of vagotomy or deems it already discarded. If the latter, who knows that they may not be right? We suggest that they might at least consider it in the paragraph entitled "Failure after Gastro-enterostomy".

The treatment of chronic ulcerative colitis covers three pages, nearly a third dealing with Hurst's polyvalent anti-dysenteric serum treatment, and Bargen's serum. We thought these had been relegated to the limbo long ago.

The section on the heart and circulation opens with an article on the principles and limitations of cardiac therapeutics which is among the most stimulating. The writer, Dr. Gilchrist, covers a lot when he states: "It is a good principle which applies with particular emphasis in the therapeutics of heart disease to treat the patient when his symptoms warrant attention, and not his physical signs". We cannot enthuse, however, about the statement (on page 638 and page 669) that "digitalis is of occasional advantage in the abolition of extra systoles when these are troublesome to the patient". As for the suggested use of digitalis (page 667) in paroxysmal ventricular tachycardia, whilst we may delight to see long held ideas toppling, and do not doubt Dr. Gilchrist's meaning from the context, it is a dangerous idea for students to have in their memory facing their examiners.

Excellent book that this is, it is a large one and of necessity contains much detail. It is a prescribed text-book for final year students at some Australian universities. Perhaps it might be wise to regard it as a book of refrence, for as such it would be invaluable to all practitioners.

PRACTICAL THERAPEUTICS.

"A COURSE IN PRACTICAL THERAPEUTICS" by Martin Emil Rehfuss is a new American book on treatment.[1] It contains a remarkable amount of information. Rehfuss begins with a brief review of general therapeutic principles and he includes a chapter on prescribing, especially pharmacopœial prescribing. He discusses the use of capsules in prescribing and gives several examples of the use of this method. Drops, powders, liquids, suppositories and diets are dealt with. Rehfuss tells the doctor what to carry in his bag.

The next chapter deals with symptomatic therapy and is arranged alphabetically: acute abdominal emergencies, acidosis, anorexia, coma, convulsions, fever, headache, and so on, up to vertigo. These 100 pages give an excellent practical approach to the diagnosis and treatment of the various symptoms discussed under the different headings. Next comes treatment for specific disorders beginning with vitamin deficiencies, and digestive tract disorders. There follow lengthy articles on the treatment of disease, with great detail in regard to classification and the necessary therapeutic procedures, including the simplest measures. For instance, in the treatment of hiccup, 73 different methods of dealing with this emergency are mentioned, with especial relation to ætiology. Although the lack of a thoroughly satisfactory alphabetical classification makes the use of the book a little more tedious than some similar books, very little time should be spent in locating the subject which it is intended to study. If any criticism could be directed at the publication, it would be for excess of detail. However, Rehfuss, Albrecht and Price are three practical physicians of great experience and the practitioner would be critical indeed if he did not appreciate the information accumulated and classified so thoroughly herein.

[1] "A Course in Practical Therapeutics", by Martin Emil Rehfuss, M.D., F.A.C.P., F. Kenneth Albrecht, M.D., Alison Howe Price, A.B., M.D., and contributors; 1948. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 11" x 8", pp. 844, with illustrations, some of them coloured. Price: £5 12s. 6d.

A YEAR BOOK OF UROLOGY.

"THE 1948 YEAR BOOK OF UROLOGY", edited by Oswald S. Lowsley,[1] is one of the volumes of the Practical Medicine Series which require no introduction to readers of this journal. The volume has been planned and published on the same lines as those adopted in previous years. It is divided into nine main sections. The newcomer to the volume will realize at once that the subject is urology and not urological surgery—nephritis and uræmia are dealt with as well as frankly surgical conditions; at the same time it must be admitted that they are viewed from the surgical point of view. This helps to give the volume an appeal to the general practitioner as well as to the surgeon specialist. The latter will find much to interest him. The section dealing with the prostate is full of interest; prominence is given, *inter alia*, to Millin's retropubic prostatectomy and to the results that have been obtained with its use. The procedure known as aortography is described as a future part of the diagnostic equipment of every urologist. The increasing use of hormone therapy is noticeable. The book concludes with a small section on gonorrhœa.

Every urologist will add this book to his library; general practitioners interested in urological conditions will find it useful.

ABDOMINAL OPERATIONS.

IT is very pleasing to see the second edition of "Abdominal Operations" by Rodney Maingot now well up to date and in one volume.[2] With the great advances in surgical technique since the original production it must have been a formidable task to rewrite most of the work.

The illustrations all through are first class, many are in colour and the publishers are to be congratulated on an excellent production.

On the whole the book is one of high standard and should prove useful not only to the beginner in surgery but to the established general surgeon. The outstanding chapters are those dealing with carcinoma of the stomach, colon and rectum. Norman Tanner has written details of the recently developed thoraco-abdominal technique for total gastrectomy and resection of the lower end of the œsophagus. Professor Harold Dew contributes a masterly chapter on hydatid disease of the abdomen. Prominence is given to Sir Hugh Devine for his work on surgery of the colon. Despite three changes of instruments and drapings the author states that infection occurs in from 2% to 5% of clean operation wounds. It was noted that there is but little comment made on skin sterilization, and it would seem that Colebrook's work in this direction has been overlooked, as also has the Medical Research Council's Memorandum Number 6. The place of vagotomy in the treatment of peptic ulceration is discussed, and there seems to be a definite use for the procedure in selected cases, provided complete vagal section has been secured. When acute pancreatitis has been found at laparotomy comment is made as to the futility and danger of incising the peritoneum over the pancreas which does not possess a capsule and therefore cannot be decompressed by such a procedure. The author commends Whipple's advice in these cases that "delayed conservative surgical management is the optimum choice". The radical operation for carcinoma of the pancreas is based on the work of Whipple and is a procedure which "demands bold thinking, careful planning and watchful care of the patient".

The after-care of major surgical procedures is always discussed and contains much useful information and mention

[1] "The 1948 Year Book of Urology", edited by Oswald S. Lowsley, M.D., F.A.C.S.; 1948. Chicago: The Year Book Publishers, Incorporated. 7" x 4½", pp. 452, with 79 illustrations. Price: $4.75.

[2] "Abdominal Operations", by Rodney Maingot, F.R.C.S. (England); Second Edition; 1948. London: H. K. Lewis and Company, Limited. 9½" x 6½", pp. 1304, with 468 illustrations. Price: 84s.

is made as to the value of the sulphonamides, penicillin and streptomycin in combating infective conditions while the value of the Ochsner-Sherren treatment in late cases of appendicitis is very clearly detailed. In regard to operative procedures for inguinal hernia only those operations which the author recommends and practises are described, but as wire sutures are coming into favour and as many surgeons use the whole skin technique, a very good discussion would have been rounded off nicely had these been detailed. There is very little redundant material, but a chapter on phlegmonous gastritis could be omitted as this is more the province of the physician than the surgeon. Also the fourteen pages given to pyloroplasty and gastroduodenostomy, which are noted as being poor substitutes for gastro-jejunostomy in the treatment of chronic duodenal ulcer, could well be greatly condensed.

GOOD HEALTH WITH DIABETES.

"GOOD HEALTH WITH DIABETES" is designed to assist the diabetic in the control of his disease.[1] Detailed instructions are given with regard to diet, the injection of insulin and the testing of the urine. The specimen menus are well designed and the directions with regard to the control of emergencies are very explicit. The warning that no diabetic should drive a motor-car after taking alcohol is very timely, because should he then suffer from an insulin reaction there is no doubt that his symptoms would be attributed to the effects of alcohol. The booklet is full of practical diabetic wisdom and should prove of great assistance to all those who suffer from *diabetes mellitus*.

PSYCHOANALYSIS.

"PSYCHO-ANALYSIS TODAY", edited by Sandor Lorand, presents a series of articles by well-known psychoanalysts together with a minority of papers by writers who have applied psychoanalytical principles to such subjects as art.[2] In all there are more than thirty contributors.

Among the practising analysts are specialists in a particular branch, including Melanie Klein, who writes on the psychoanalysis of children. This is the most vital field of research today, application of Klein's discoveries having already led to satisfactory results in the treatment of adult psychotics; the pertinent observations were made in the study of the depressive and paranoid states which occurred in her infant patients. Klein considers that these states occur in all children, that it is a matter of degree whether they are sufficiently crippling to make treatment advisable in any particular child, and that every child would benefit from psychoanalysis. She writes: "When we see all this, we are ready to believe that what would now seem a Utopian state of things may well come true in those distant days when as I hope child-analysis will become as much a part of every person's unbringing as school education is now." If this is so, prophylactic analysis should reduce the incidence of all emotional illnesses—psychoses, psychoneuroses, perversions, addictions, criminality, and psychosomatic complaints.

The inclusion in the book of several papers on psychosomatic illnesses should interest all practitioners who treat people rather than diseases, even if they do not agree with Klein. Ferenczi writes concerning Freud's discoveries: "It is striking that such substantiations come not only from psychiatrists, but from circles of internists, gynæcologists, pædiatricians, dermatologists, and so on. They state that many a problematical case in their field has become intelligible and accessible to therapy only because of a psychoanalytical explanation."

Flinders Dunbar states that in 80% of serial admissions to a general hospital the psychoanalytical approach was important for both diagnosis and treatment. He discusses the types of case that are most suitable for psychoanalysis, but indicates that any disability at all may have associated emotional causes. He considers, however, that only about half the number will receive much benefit from psychoanalysis, especially if structural changes have supervened, and that especially in the latter physical treatment may be the more practical.

O. S. English also warns against disregarding indications for and against psychoanalysis.

S. E. Jelliffe has written a paper entitled "Psycho-Analysis and General Medicine".

Franz Alexander, the first analyst to specialize in psychosomatic research, has an article on "The Development of Ego-Psychology".

One of the most fruitful applications of psychoanalysis to an auxiliary science is in the sphere of anthropology. Gaza Roheim, who underwent analysis himself, has for many years carried out field studies in several parts of the world, including Central Australia, together with psychoanalyses of individuals in these different communities. His experiences confirm Freud's main anthropological formulations, but he has also amplified and modified them through his own discoveries. In addition Roheim has tried to broaden psychoanalytical theory by reapplying to it conceptions derived from anthropology, and also from biology out of which both psychoanalysis and anthropology stem.

Another modification of psychoanalytical application that is occurring as a result of experience is with regard to the emotional education of children. From the article "Child-Parent Relationship" the conclusion may be drawn that unanalysed parents who attempt to apply psychoanalytical principles in bringing up their children will only partially succeed in their aim and will continue to affect their offspring adversely because they remain unaware of their own emotional handicaps. If Klein is right, even the children of thoroughly analysed parents would benefit from prophylactic analysis because of the unreal psychological attitude to parents from which every infant suffers.

[1] "Good Health with Diabetes", by Ian Murray, M.D., F.R.F.P.S.G., F.R.C.P.E., and Margaret B. Muir, S.R.N.; 1947. Edinburgh: E. and S. Livingstone, Limited. 7¼" × 4¾", pp. 48. Price: 2s.

[2] "Psycho-Analysis Today", edited by Sandor Lorand, M.D.; 1948. London: George Allen and Unwin, Limited. 8½" × 5½", pp. 424, with few illustrations. Price: 25s.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Skin Diseases in General Practice", by F. Ray Bettley, T.D., M.D., F.R.C.P.; 1949. London: Eyre and Spottiswoode (Publishers), Limited. 8½" × 5¼", pp. 264, with 96 illustrations. Price: 21s.

One of "The Practitioner Handbooks".

"Textbook of Midwifery", by Wilfred Shaw, M.A., M.D. (Cantab.), F.R.C.S. (England), F.R.C.O.G.; Third Edition; 1949. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 468, with 239 illustrations. Price: 22s. 6d.

Intended primarily for undergraduate students.

"Practical Aspects of Thyroid Disease", by George Crile, junior, M.D., F.A.C.S.; 1949. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 7¾" × 5¼", pp. 380, with 101 illustrations. Price: 42s.

Presents "only the salient features" of thyreoid physiology and diseases.

"Forensic Medicine: A Textbook for Students and Practitioners", by Sir Sydney Smith, C.B.E., M.D. (Edinburgh), F.R.C.P. (Edinburgh), D.P.H., and Frederick Smith Fiddes, O.B.E., M.D.; Ninth Edition; 1949. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 676, with 173 illustrations. Price: 30s.

Replacing the eighth edition of 1943.

"Handbook of Diseases of the Skin", by Richard L. Sutton, M.D., and Richard L. Sutton, junior, M.D.; 1949. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9" × 6", pp. 772, with 1057 illustrations. Price: £4 14s.

Intended for medical students, practitioners and specialists in dermatology.

"Répercussions sur l'enfant des maladies infectieuse de la mère pendant la grossesse", by F. Bamatter; 1949. New York: S. Karger, Limited. 9½" × 6½", 24 illustrations. Price: SFR. 7.50

Makes particular reference to maternal rubella.

"Essentials of Orthopædics", by Philip Wiles, M.S. (London), F.R.C.S. (England), F.A.C.S.; 1949. London: J. and A. Churchill, Limited. 9¾" × 6", pp. 508, with 365 illustrations and 7 coloured plates. Price: 42s.

Intended as an explanation of the physiological and pathological basis of orthopædics and its application to diagnosis and treatment.

The Medical Journal of Australia

SATURDAY, JULY 2, 1949.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

PROGNOSIS IN GASTRIC CANCER AFTER RESECTION.

IN a discussion on gastric cancer in these columns on May 15, 1948, we referred to the generally poor prognosis and quoted Wangensteen's statement that 92% to 98% of patients who have gastric cancer will die of the disease within five years; on the other hand, we pointed out, it has been calculated that, of patients who survive resection for gastric cancer for a period of five to seven years, the subsequent life expectancy is about the same as for normal persons. It would then be most useful if we could find reliable criteria on which to base prognosis after resection of the growth and in particular to know when an individual patient was likely to survive the crucial five-year period. R. Schindler[1] made use of the classification of gastric carcinomata into four gross types, as first described by Borrmann in 1901, and tentatively concluded that determination of the Borrmann type of the growth before operation by means of radiography and gastroscopy was of value in the assessment of prognosis. Borrmann's types are: I, sharply demarcated polypoid carcinoma; II, sharply demarcated ulcerated carcinoma; III, partly infiltrating carcinoma; IV, diffusely infiltrating carcinoma. Schindler noted that after resection of carcinoma there was a significantly greater survival rate among patients with lesions of the "limited" types (types I and II) as compared with those having lesions of the "infiltrative" types (types III and IV); indeed, none of his patients in the latter group survived for five years. Schindler presented his findings with some diffidence and declined to draw any firm conclusions. However, he urged that others should carry out similar research, stressing the importance of knowing when and when not to advise surgical intervention. He felt that if his tentative conclusions were confirmed one might become reluctant to attack infiltrative forms surgically unless the respective tumour was very small. G. E. Moore, D. State, R. Hebbel and A. E. Treloar[2] have followed up his work with the analysis of a much larger series of cases, and have thrown considerable doubt on the usefulness of the Borrmann classification. They have kept a complete record of 124 patients whose stomachs, removed at operation between 1938 and 1943 for gastric carcinoma, were available for reexamination and have analysed the relative importance of Borrmann typing and the presence of metastases in relation to the three-year and five-year survival rates. Their first conclusion is that the presence or absence of demonstrable metastases in regional lymph glands among patients subjected to gastric resection for carcinoma has a greater prognostic value than has the Borrmann type of the tumour. Their results by no means uphold the hopeless prognosis suggested by Schindler for patients with infiltrating carcinomata and they assert that these patients have a reasonable chance of survival if no metastases are present. The position appears to be (and this is their second conclusion) that the Borrmann type affects the prognosis in groups of cases to the extent that "the limited tumours provide a proportionately large number of patients free of metastases while the infiltrating tumours which are more numerous are more likely to have metastases". The Borrmann types alone, even when determined post-operatively, are "inadequate indicators of the wisdom of surgical procedures", and so attempts to predict the survival of patients with carcinoma of the stomach by the gastroscopic typing of their lesions are not justified. The final conclusion of Moore and his colleagues seems, as it were, to "blanket" the whole discussion, but none the less it follows from their investigation and makes sense: "The presence or absence of metastases cannot be accurately determined pre-operatively and no patient should be denied operation because of the type of tumour he may be determined to have." This is, of course, in line with the strong bias in favour of surgical intervention expressed in Livingston and Pack's classical book "End-results in the Treatment of Gastric Cancer", and gains in weight as the technique of resection develops.

A different approach to this problem has been made by S. N. Maimon, W. L. Palmer and J. B. Kirsner,[1] who, instead of studying a full group of patients after resection, concentrated on those who actually survived for five years or more and sought to find the factors responsible for the survival. These five-year survivors numbered 30, being the remnant of 115 patients who survived gastric resection coming from a total number of 377 patients with gastric carcinoma. The first striking point is that half of the five-year survivors had had symptoms of over a year's duration before operation as against only one-third of the original group, and the findings of other investigators are quoted in which the proportion of five-year survivors was greater amongst those whose history was long than amongst those whose history was short. The statement is then made: "These observations raise the question of the validity of the great emphasis placed on 'early diagnosis'." A number of related factors are mentioned, but this question is left unanswered. This would seem to be dangerous. The rather curious fact noted on the relationship of length of survival and length of history must be accepted, but a number of possible explanations spring to mind, and at least until the facts are much more carefully analysed the drawing of conclusions is unjustified. It is certainly undesirable and illogical, especially from the point of view of educating the public,

[1] *Surgery, Gynecology and Obstetrics*, October, 1946.
[2] *Surgery, Gynecology and Obstetrics*, November, 1948.

[1] *The American Journal of Medicine*, August, 1948.

to lessen in any way the emphasis on early diagnosis. It would be valid and right for patients to understand clearly that early diagnosis does not ensure a good prognosis and that a long history is no warrant for despair, but surely, no matter what the comparative findings in a group, the prognosis in any individual case will not be improved by delay in either diagnosis or treatment. No doubt Maimon and his colleagues would agree with this, but it is important to have considered the issue before going on to their main point, the great prognostic importance of the fundamental biological characteristics of the tumour. The 30 tumours were first of all classified according to Borrmann and 26 were found to belong to types I and II; four belonged to type III and none to type IV. A comparison of these findings with the total incidence as described by Schindler appears to support the value of the Borrmann classification in relation to prognosis, and Maimon and his colleagues apparently feel that it is of some use, though they record that in a comparison of the five-year survivors with a group who survived for less than one year after resection, the correlation was not so striking. Of most interest are their histological studies, which are reported in detail in a paper in whose authorship P. E. Steiner joins Maimon, Palmer and Kirsner.[1] Three microscopic features were found which were correlated with long survival. In order of importance they were: sharp circumscription of the tumour; two special histological types of cancer, a detailed description of which cannot be included here; a characteristic retrogressive change in tumour cells occasionally present and resembling that found in prostatic carcinoma after orchidectomy. These factors were considered to be more reliable in predicting outcome than was histological grading or macroscopic typing or a combination of both. The important comment is made that five-year survival after gastrectomy for cancer may be due to cure by complete extirpation or to slow rate of recurrence; the relative importance of these two factors cannot be determined until the ultimate outcome is known. It is interesting to note that seven of the thirty five-year survivors had metastases, but none of them survived more than twelve years. There is a great deal more in all of these papers on which we might comment, but the outstanding point remains that no sure method of assessing prognosis is yet known. A very guarded opinion may be formed before operation, evidence of considerable value may be obtained when the resected stomach is available for examination, but we need to know a great deal more about the essential nature of cancer and the rate of cancer-cell growth before the problem will be solved.

[1] *The American Journal of Pathology*, September, 1948.

Current Comment.

AN EPIDEMIC OF THYREOTOXICOSIS.

ONE of the recollections of the war of 1914-1918 is that an increase in thyreotoxicosis among the peoples involved was surprisingly not encountered. Perhaps the word "surprisingly" begs the question of ætiology, but at this time there was a general awakening of interest and understanding in those conditions now often called psychosomatic diseases, even though this did not correct the undue emphasis of the "organic" point of view in the iatrogenic "soldiers' heart". But it has been and still is realized that stress plays a part in hyperactive disturbances of the thyreoid, and it would not be strange if war produced a rising number of sufferers from hyperthyreoid states. Kurt Iversen has published a critical account of an epidemic wave of thyreotoxicosis in Denmark during the recent war of 1939-1945.[1] This may be accurately described as peculiar, as it does not seem to have been paralleled elsewhere among the peoples who bore the weight of oppression during those years. Meulengracht has already given an account of this wave of thyreoid disease in 1943, and while this account was not complete, as subsidence of the increase was not seen till after the end of the war, we can be assured that in the hands of this famous observer and other exponents of Danish medicine the records would be full and reliable. Iversen found that it was very difficult to form an accurate estimate of the incidence of thyreotoxicosis in the country, as so many cases might not be included in hospital records. He therefore has taken the figures for the municipality of Copenhagen for the period 1938-1947. Records from all the hospitals in Denmark show that there was a rise in thyreotoxicosis from 1931 onwards, which was suddenly accentuated in 1941 until the case incidence between 1941 and 1944 was three to four times its pre-war level. Iversen's Copenhagen figures show that the percentage of incidence in relation to the population rose from 0·19 in 1938 to 0·84 in 1943, maintained this level with but slight variation till 1944, fell to 0·52 in 1945, and in the next two years after the war receded to the original value. Scrutiny of records showed that the increase was greatest among those with the severe type of the disease both with and without exophthalmos, the latter being by far the commoner. This led to an inquiry into the symptoms, which showed that a change appeared in symptomatology during the war, which was responsible for this increase in the exophthalmic type. Investigation of the morbidity rates for other countries during the war has shown that, although a steady rise has been taking place for a number of years, nothing like this sudden wave in Denmark has been seen. Indeed, it would appear that in Holland and Belgium there has been a decrease in the numbers. In Norway a steady rise persisted up to 1941, but thereafter a fall occurred, which coincided in time with the nutritional crisis. No epidemic wave or striking increase was found in other countries not in the continent of Europe.

The author can offer no satisfactory explanation for this experience in Denmark. The existence of severe psychic strain is admitted; this was especially heavy when the German occupation added terrorism to its burdens in 1944 and 1945, but the curve shows no appreciable change. Psychic trauma was especially investigated in many of the patients, and only in some 5% could any strikingly severe personal strain be discovered from the patients' history. The strong resemblance to an infectious epidemic suggested the possibility of a relation to some infective state, but none could be found. Cold has been cited as an inciting factor, and Iversen quotes an epidemic wave which occurred in Minnesota in 1924 to 1926, when severe cold was experienced. In the present instance it was noted that three extremely bitter winters coincided with the period of highest incidence in Denmark, but Iversen does not venture to draw any conclusions from this. Changes in nutrition are obviously of importance, but an examination of the diets consumed during these years does not disclose a fall or alteration in balance or in protective substances significant enough to provide the answer. It would seem, however, that the solution may lie in the dietary intake of the people over this period, especially as a true estimate of diet is very hard to make under the prevailing conditions. Iversen remarks that some change in the content of antithyreoid factors in the national dietary might give the explanation. Recalling some of the experimental work on animals which has emphasized the significance of goitrogenic substances in their diet, this would seem to be a promising line of human research should a similar epidemic occur under

[1] *The American Journal of the Medical Sciences*, February, 1949.

conditions less harassing. Since Iversen's article appeared a further analysis of this outbreak has been made by E. Meulengracht.[1] He agrees with Iversen as to the difficulty in assigning any cause, but suggests that the hypothesis of infection is worth some consideration. He remarks that there are many objections to such an idea, but refers to some pre-war epidemics in all of which geographical localization was a feature. Alterations in sex and age incidence were noted in these, and also aberrations from the usual patterns of symptomatology; these have been also pointed out by Iversen, as we have seen. One curious coincidence in the present instance was that two diseases simultaneously predominated in the medical wards of Bispejerg Hospital at this time, a severe subacute hepatitis of virus type, and "a form of thyreotoxicosis that nobody was prepared to accept as such". These parallel outbreaks presented curves of incidence of striking similarity, but nothing was found to suggest any causal relationship. Meulengracht remarks that attempts to transmit thyreotoxicosis in the past have been limited to research on toxic factors, and their failure proves nothing. He quotes Means as stating that this strange epidemic is "just a brutal fact" which calls for an explanation. It is more: it is a challenge.

THE THERAPEUTIC POSSIBILITIES OF BACTERIAL FIBRINOLYSIN.

ONE of the striking pathological features of tuberculous meningitis is the presence of a gelatinous exudate at the base of the brain. This has been a cause of difficulty in handling that lethal disease, and the occurrence of a "dry tap" in the performance of lumbar puncture, necessitating the use of the cisternal route, is familiar to those who have attempted its treatment. It has also been a source of inquiry into the mechanism of the disease, and it is now generally accepted that the meningeal affection is due to local spread from a tuberculous nodule of earlier vintage. The curious meningeal reaction is thought to be due to allergic response, as the meninges at the base of the brain are more or less suddenly assailed by a massive infective dose. It is known, too, that tuberculous meningitis cannot be produced experimentally by introducing the live infection into the cerebral circulation. However, it is the therapeutic difficulties caused by this propensity of the cerebro-spinal fluid to form fibrinous webs that interest us at the moment, as the suggestion has been made by I. A. B. Cathie that a fibrinolysin of bacterial origin might be used to inhibit fibrin formation within the subarachnoid space.[2] Heparin has been used for this purpose, but it forms a deposit with streptomycin, to avoid which special methods are needed. The results, according to Cathie, have not been very satisfactory, and there is in addition the drawback that no special lytic action on the fibrin already formed is exerted by heparin. Usually, as Cathie points out, fibrinous webbing has already formed when the diagnosis is made. Some pathogenic strains of hæmolytic streptococci produce a lysin capable of dealing with human fibrin clots. The yield of this lysin is variable, but Cathie has used a strain known as H.64 which produces an abundant and consistent yield of fibrinolysin. Details of the preparation are given in the article; the fibrinolysin is obtained from a broth culture, adsorbed onto alumina, and eluted from this in a buffered solution. The final product is sterilized by passage through a bacterial filter. Investigation of this material has shown that it is stable, and may be stored for at least fourteen days without loss of activity. Assay has also been carried out by a specially devised method, depending on the capacity to dissolve a standard clot of human fibrin in a standard time. It has been shown that the action of the lysin is quantitative. Before the effect of this substance in therapy was tried experiments were made on its power on pieces of exudate taken from the basal region of the brain of persons who had died from tuberculous and coliform meningitis. In the tuberculous cases lysis was almost complete, only a fine mesh being left. Pieces of brain and normal meninges were used as controls, lest some lytic action should be exerted on other tissue, but incubation for a month left these unaltered. Care was also taken to ensure that the introduction of fibrinolysin into the theca would not cause an undue reaction. Only a small increase in the white cells of the cerebro-spinal fluid occurred, and although there was a slight rise in the polymorphonuclear cell count and in the protein content of the fluid, this was no greater than that found after the injection of streptomycin into normal membranes. Further, the fibrinolysin solution formed no deposit with streptomycin sulphate, the salt which was used in the clinical trials. In these trials the dose of lysin was chosen empirically; also the frequency of administration was a matter of general judgement. Only one batch of lysin was found to show any toxic properties, as evinced by rise in the cell count in the cerebro-spinal fluid. Otherwise injections could be made into the subarachnoid space by all routes without the production of any untoward signs. No exact clinical results are published as yet. Cathie states that the results have been sufficiently encouraging to warrant a further trial on more extended lines, but the period of time over which actual patients have been treated is too short for the drawing of deductions. This work may have in it the germ of a valuable idea. Since the attention of the world has been drawn to the possibilities of using the metabolic activities of bacteria and moulds several useful substances have been given to the clinician, and help would be welcome in the treatment of a disease that is fatal because of its unfortunate anatomical location.

[1] *Archives of Internal Medicine*, February, 1949.
[2] *Journal of Clinical Pathology*, February, 1949.

FURTHER REPORTS ON CHLOROMYCETIN.

CHLOROMYCETIN has created a particular interest of its own among the antibiotics by its action in scrub typhus. Preliminary reports on this were discussed in these columns on September 18, 1948; subsequent reports have apparently supported the hopes then expressed. Another disease lacking specific therapy for which chloromycetin has been used with encouraging results is typhoid fever. In a preliminary report published in America last year T. E. Woodward, J. E. Smadel, H. L. Ley, R. Green and D. S. Mankikar[1] stated that during their investigation of the chemotherapeutic value of chloromycetin in the treatment of scrub typhus on the Malayan peninsula, they decided to test the efficacy of the drug in the treatment of typhoid fever, which was endemic in the area and of a clinically severe type. The report deals with the results of treatment in ten cases of the disease, the diagnosis being confirmed in all cases by blood culture; treatment was commenced during the first two weeks of fever, mostly about the tenth day. Chloromycetin was given by mouth to a total average dosage per patient of 19·1 grammes over a period of 8·1 days. It was tolerated well and no clinical evidence of toxicity was observed. Evidence of improved general condition and lessened toxic effects was usually apparent within twenty-four hours after the start of specific treatment, and increasingly thereafter. In the first seven cases the temperature reached permanently normal levels after three days of treatment. The mean in the ten cases for the duration of fever after the beginning of chloromycetin treatment was 3·5 days. Daily blood culture was possible in only eight of the ten cases, but in these it was carried out daily for five days after the beginning of treatment with negative results in all cases. No patient was discharged from hospital until stool culture had yielded three consecutive negative results; in two cases positive results from stool culture were obtained during convalescence, in one on the seventeenth day after institution of therapy and in the other on the fifth and twelfth days; subsequent results were negative. Urine culture yielded consistently negative results at all stages. Two patients suffered relapse with bacteriæmia, after ten and sixteen days respectively, but responded promptly to a second course of chloromycetin.

[1] *Annals of Internal Medicine*, July, 1948.

As the report points out, it is of interest to note that the organisms isolated during the recurrences were as sensitive to chloromycetin when tested *in vitro* as were those isolated initially. Two serious complications occurred, intestinal perforation on the second day of normal temperature, and massive intestinal hæmorrhage on the fourth afebrile day; both patients recovered after a more or less stormy course, one after supplementary therapy with streptomycin and penicillin and the other after blood transfusion. Eight control cases form a striking contrast; one patient died from his illness on the seventeenth day, and the average total duration of fever in the other seven cases was 35 days; in contrast with the average duration of fever after institution of chloromycetin therapy on the ninth day of illness (3·5 days), the duration in the untreated patients after the ninth day was 26 days.

The use of chloromycetin in the United Kingdom has been much more recent and is apparently still hampered by dollar difficulties. The first report of its use, in a single case, was made by F. Murgatroyd,[1] the patient's response having been satisfactory up to the time of the report. W. H. Bradley,[2] Senior Medical Officer of the Ministry of Health, has now prepared a preliminary communication on its use in an outbreak of typhoid fever in a Berkshire village, where some of the people ate food infected with *Salmonella typhi*, or rather, to quote the report more accurately, "an aliment" infected with *Salmonella typhi* "was consumed by some of the inhabitants". Of 22 patients (all "consumers" of the "aliment") admitted to hospital, ten were treated with chloromycetin, selection being by the strict "alternate case" method. Two very elderly patients, one treated and one a control, died soon after admission to hospital. In all the remaining nine treated patients signs of resolution were obvious within forty-eight hours; seven were apyrexial by the third day of treatment and the other two had normal temperatures throughout the fourth and fifth days respectively after treatment started. Thereafter resolution has been complete in all cases. Constitutional disturbance was affected rather more rapidly than the temperature, the influence on the severe headache being dramatic. Bradley naturally declines to attempt any evaluation of the drug's effects at such an early stage, but the results so far appear to correspond to the favourable response observed over a much longer period by the American workers. The important point is that undeniable benefit has resulted from the use of an antibiotic in typhoid fever. Chloromycetin may not provide the final answer. Indeed, speaking at a meeting of the New South Wales Branch of the British Medical Association on May 26, 1949, J. Kempson Maddox stated that he had been informed that investigations were being carried on at the Johns Hopkins Hospital into a possibly adverse effect of chloromycetin on the kidneys. However, as he pointed out, other effective antibiotics are coming to light, and if chloromycetin should have to be discarded, we may reasonably hope that a more satisfactory successor will be found.

It is interesting to note, on the other hand, that the United States army medical authorities are apparently still very interested in chloromycetin. Recent information from the office of the Surgeon-General in Washington reveals that the Army Medical Department Scrub Typhus Research Unit has returned recently to Malaya, where its members carried out the significant work on scrub typhus and typhoid fever already referred to. They have taken to Malaya a new synthetic chloromycetin developed by the Parke, Davis Laboratories. It is intended, firstly, to try this new form of the drug on native patients infected with scrub typhus, and to compare its efficacy with the natural mould derivative; secondly, to investigate its prophylactic value, more particularly for combat troops landing in typhus areas; thirdly, to compare the effect of the new synthetic drug with that of the natural form in the treatment of typhoid. The immediate hope of the team is to demonstrate that the synthetic drug may be considered safe and effective in the treatment of humans, that prophylaxis may be achieved in typhus and similar infections for which no vaccines have been available, and that the established period of protection may be extended without toxicity or other after-effects. The team is apparently optimistic and we hope that their optimism is justified. But we must not assume the results until they appear, and this even more because of the striking possibilities the drug offers. Typhus in its various forms and typhoid are still common in certain parts of the world, and typhus in particular is greatly feared. A readily available commercial preparation of chloromycetin which could conquer these diseases, and perhaps others, would have an effect that is difficult to appreciate fully. It is startling to learn that in 1942 almost 100,000 cases of epidemic typhus were uncovered in North African territories where Americans were serving, that over a million cases occurred in Italy in 1943 and 1944, and that great numbers of cases were found in Germany after the war and an appreciable number even in Western European countries where it was previously unknown. If chloromycetin fulfils its promise in this and similar diseases and is found safe, the members of the research unit will have achieved greatness.

[1] *British Medical Journal*, May 14, 1949.
[2] *The Lancet*, May 21, 1949.

HONEYCOMB LUNGS.

CONSIDERABLE interest has been taken in cystic disease of the lungs, and in Australia, as elsewhere, physicians and radiologists have been active in recognizing different forms of this condition. The name "honeycomb lungs" indicates the uncertainty as to the ætiology of cystic disease, and its use is recommended by Neville Oswald and Thomas Parkinson for this reason.[1] An ætiological basis for terminology is no doubt ideal, but to adopt such a basis on a wide scale would need a degree of scientific prevision that none of us possess. Hence these writers draw attention to the fallacies inherent in the use of such terms as "congenital cystic disease", "cystic emphysema" and the like by reverting to the older practice of using a descriptive term. They are careful to point out that they refer only to a single variety of cystic disease of the lungs in which thin-walled cysts are scattered throughout the substance of both lungs, none being larger than one centimetre in diameter. They have collected sixteen cases, of which six had the common feature of being associated with a general medical disorder. The remaining ten cases differed in not having any certain connexion with any extrapulmonary disease. The name has the virtue that it brings a clear picture before the eyes, and suggests also the absence of any systematic anatomical description. Such varied conditions as xanthomatosis, tuberose sclerosis, biliary cirrhosis and pituitary disorders have been recorded in the literature as pathological states with which honeycomb lungs may be associated.

The six patients grouped together in Oswald and Parkinson's series include one with xanthomatosis, two with hepatic disorders, one with tuberose sclerosis, and two with pituitary disturbances. The type associated with pulmonary lipoidosis, as might be expected, shows also infiltration of bones, lymph nodes and the dura. It is thought to be a later stage of interstitial infiltration of the fibrotic type. The two patients with liver disease were young children. In each instance death followed a brief period of severe dyspnœa, with signs of progressive failure of the right side of the heart, which was also the cause of death of the first patient. The patient with tuberose sclerosis was aged thirty-one years, and had had shortness of breath for five years. With the coexistence of *adenoma sebaceum*, subungual fibromata and radiological signs indicative of interstitial reticulation it seems logical to regard the lesions as part of one process, especially as there were signs and symptoms suggesting involvement of other organs, such as the heart and the kidney. The pituitary patients were aged fifteen and thirty-six years respectively. One had a pituitary dystrophy, the other

[1] *The Quarterly Journal of Medicine*, January, 1949.

had *diabetes insipidus*. Both had dyspnœa, and had previously had a spontaneous pneumothorax.

The remaining cases of uncertain ætiology are also described by the authors, and may be summarized in the following way. Spontaneous pneumothorax and failure of the right side of the heart were seen in this group, the former accident being more common in the lower age group, and the latter in the higher age group. It was thought possible that some subdivision of this series might be possible, as none of those who died of heart failure had previously had pneumothorax, suggesting a difference in the nature of the pulmonary condition. In all eight of Oswald and Parkinson's patients suffered from spontaneous pneumothorax, and in five it was bilateral. The remaining eight had dyspnœa that was either progressive or fatal. These features are also found in the records published in the literature. The authors can give no light on the problem of causation. Sometimes the condition seems due to congenital causes, but secondary factors of a mechanical or inflammatory nature are thought to be responsible in other varieties. None of these patients presented any signs of other developmental abnormality. The object of the authors is to draw attention to the obscurity still surrounding the subject, and to emphasize that honeycombing of the lungs may arise in a variety of conditions which affect the body widely.

LIGATION OF THE COMMON CAROTID ARTERY.

THERE are a number of indications for ligation of a carotid artery, the most notable being the presence of a leaking intracranial aneurysm, but the operation has mostly been approached with diffidence. The work of Lambert Rogers in this field is well known, as he has for some years now been reporting his research into the relevant functional anatomy, particularly that of the circle of Willis, and the development of appropriate surgical technique. Nearly two years ago, in a paper dealing with the ligature of arteries in general,[1] he discussed the most satisfactory procedure for dealing with a carotid artery and emphasized the greater safety in ligating the common carotid artery in preference to the internal carotid, because of the collateral pathways left available in the former case through the external carotid. He also referred to the advantages of division of the artery between ligatures as against ligation in continuity, namely, the prevention of recanalization, the decreased likelihood of peripheral vasospasm because of division of the sympathetic fibres in the adventitia, reduction of the danger of secondary hæmorrhage and the lessened risk of embolism from a clot displaced through the pumping action retained with ligation in continuity. The undesirability of tying the accompanying jugular vein was pointed out; although in a limb the accompanying vein usually needs to be tied, electroencephalography has shown that in the case of the great vessels of the neck this step will increase cerebral anoxia. In view of this and other papers which Rogers has already written on this subject it is now of interest to see his report of 19 consecutive ligations of the common carotid artery personally carried out.[2] Adhering to his principles of division rather than ligation of the artery in continuity (except in the three earliest cases) and the submission of each patient to his tolerance test designed to ascertain "the competence of the circle of Willis as an anastomosis to give rise to a collateral blood supply", he has obtained an essentially satisfactory result in every case. None of the patients had any permanent cerebral disturbance following the occlusion; transient loss of consciousness and hemiplegia occurred in one case. One patient died from bronchopneumonia, but the operation must be counted as successful. Rogers adds to his series of 19 cases of common carotid artery ligation, 24 others from several sources, and states that in only one case, in which there were dual intracranial aneurysms, was there any undesirable result. By contrast, among 51 collected cases of internal carotid artery ligation (two of them Rogers's own) there were 12 with cerebral complications (one of Rogers's two cases being included) and eight patients died. His conclusion, then, is that ligation of a common carotid artery is relatively safe in a fit person who survives the tolerance test (though the artery should be divided, not ligated in continuity), but ligation of an internal carotid artery is dangerous and to be avoided as a primary procedure. If it is proposed to ligate the internal carotid in the neck, Rogers recommends that the common carotid should first be divided and then, some weeks or months later, the internal carotid artery may be resected. However, he obviously does not like the ligation of the internal carotid and his opinion warrants respect, just as does his confidence in the relative safety of division of the common carotid.

[1] *The British Journal of Surgery*, July, 1947.
[2] *The Lancet*, June 4, 1949.

YET ANOTHER ANTIBIOTIC—NEOMYCIN.

No sooner has the puzzled practitioner rearranged his concepts concerning the latest and most promising antibiotic, than he learns that still another and apparently a better has managed to swim into the ken of the chemotherapist. It is certainly remarkable that penicillin holds its place in treatment despite the rivalry of well over a hundred competitors. Just as carbolic acid, introduced by Lister as the first antiseptic, served the surgeons of a generation and on the whole served them well, so penicillin holds pride of place in the treatment of many infections and is likely to do so for some years to come, being "exhibited" in every possible manner from intravenous injection to the use of lozenges, ointments, powders and even chewing gum. The isolation of streptomycin was announced some five years ago and it was soon recognized that it was highly effective against tuberculosis organisms. "Thus for the first time", so an American article has remarked, "in the history of human tuberculosis, a drug was found which could be used in the treatment of tuberculosis by means of chemotherapeutic agents and which pointed to the possibility of finally eradicating the white plague of man".[1] But as invariably happens with each new and highly acclaimed medicinal agent, further experience brought to light certain shortcomings, chief amongst which were neurotoxic potentialities and, most important of all, the development of resistant strains amongst the infective organisms against which it was pitted. Recent experiments rather indicate that the toxic reactions can be side-stepped, at least in considerable degree, by the use of dihydrostreptomycin, a product of reduction. But the unhappy apparition of resistant strains still haunts the use of this antibiotic in the treatment of tuberculosis. In the recent search for new compounds particular attention has been paid to those that would be effective against streptomycin-resistant bacteria, especially the resistant strain of *Mycobacterium tuberculosis*. The claim that this search has succeeded has been made and to this antibiotic the name neomycin has been given.[2] Like several others, the organism producing neomycin was isolated from the soil and shows some affinities with a culture prepared in 1915 and now named *Streptomyces fradii*.[3] Neomycin is a basic substance most active in alkaline solution. It is thermostable and soluble in water but not soluble in the usual organic solvents. Amongst the desirable properties claimed are that it shows similar activity against both streptomycin-sensitive and streptomycin-resistant bacteria, that it is specially successful with tuberculosis organisms, that it has a limited toxicity to animals and that it is active *in vivo* against Gram-positive and Gram-negative bacteria. As this substance has not to date been obtained in crystalline form little can be said about its chemical constitution. The results of further research are promised at a later date.

[1] *Science*; see below.
[2] "Neomycin, a New Antibiotic Active against Streptomycin-resistant Bacteria including Tuberculosis Organisms", S. A. Waksman and H. A. Lechevalier, *Science*, March 25, 1949, page 305.
[3] S. A. Waksman and R. E. Curtis: *Soil Science*, Volume I, page 99, 1916.

Abstracts from Medical Literature.

PATHOLOGY.

Rapid Deceleration and Rupture of the Aorta.

ISAAC TANNENBAUM AND JOHN A. FERGUSON (*Archives of Pathology*, April, 1948) report two cases of rupture of a histologically normal aorta in which the damage to the thoracic cage was minimal. Theories of such rupture are reviewed, and the authors state that in these cases it is most probably due to forces exerted by rapid deceleration. The theory of the effects of rapid deceleration, which was brought out to explain rupture of organs in military aircraft accidents, can be applied to rupture of organs in civilian motor-car accidents in which there has been sudden arrest of forward motion. Therefore, in such cases, even in the absence of evidence of injury to the thoracic cage, the possibility of rupture of the aorta should be considered.

Parafollicular-Cell Adenoma of the Thyreoid Gland.

L. BAKAY, JUNIOR (*Archives of Pathology*, April, 1948) describes three cases of goitre of a new histological type. The cells form rosettes around the capillaries, resulting in dense networks of a parenchymal structure and poor in colloid. The cells are large; their protoplasm is granular; their nuclei are vesicular, swelling at the beginning and later shrinking. They are similar to the "oncocytes" described by Hamperl, which the author considers to be degenerate varieties of the parafollicular cells of the thyreoid gland. The type of goitre described here is identical with the Hürthle cell tumour of Wilensky and Kaufmann, but different from the Langhans adenoma.

Congenital Cardiac Anomalies and Pulmonary Vascular Lesions.

KENNETH J. WELCH AND THOMAS D. KINNEY (*The American Journal of Pathology*, July, 1948) report a study of the lungs from 67 patients having congenital cardiac anomalies, in which there was a left-to-right shunt to determine the effect of the altered hæmodynamics on the pulmonary vascular bed. The lesions were graded according to the degree of intimal proliferative, intimal hyaline, and medial changes found. Control groups of ten cases for each of the first seven decades of life were examined to determine the effects of aging alone on the pulmonary vessels. The incidence of pulmonary atherosclerosis was found to be remarkably high in this group. Twenty-five cases of patent *ductus arteriosus* with significant defects were studied. With one exception the changes in the pulmonary vascular system were no greater than changes in the control group in comparable ages. In all cases the changes present were atherosclerotic in type, and no medial lesions were found. Twenty-five cases with interauricular septal defects of 0·8 centimetre or more were selected. In uncomplicated cases the pulmonary vascular lesions were not greater than in the control group. In nine cases complicated by rheumatic mitral disease, marked and constant atherosclerosis was found in excess of the control group. Eleven cases with isolated interventricular septal defects were studied. In most of these the defects were of less than one centimetre and the pulmonary vascular lesions were not greater than those of comparable ages in the control group. In one case with a defect of two centimetres marked atherosclerosis of the pulmonary artery was observed by the authors. Six cases having a combination of lesions giving a left-to-right shunt were studied. The degree of pulmonary atherosclerotic change in each case was proportionate to the age and to the magnitude of the shunt. The common factor in the production of pulmonary vascular lesions in the occasional cases in each of the above groups appeared to be a marked increase in the pulmonary blood flow.

Distribution of the Lymphatics of the Human Kidney.

ARNOLD J. RAWSON (*Archives of Pathology*, March, 1949) states that the lymphatic channels of the human kidney have been traced in a case in which permeating carcinoma cells made these channels easily visible. The investigations indicate that the lymphatic channels begin blindly in two locations, namely, closely adjacent to the capsule of Bowman, and beneath the mucosa of the papilla. From these origins two networks arise which accompany the arterial and the venous vessels of the kidney. The network arising in the medulla drains upward, toward the arcuate vessels, whereas that beginning near Bowman's capsule drains in the opposite direction. The two become confluent about the arcuate vessels. No lymphatic channels are demonstrable in the glomeruli, about the afferent or the efferent arterioles, or about the intertubular capillaries. If such networks exist, their calibre is too small to permit carcinoma cells to permeate them. Especially noteworthy is the close association of the lymphatic channels and the large thin-walled veins of the outer half of the renal cortex. It is believed that these veins are expansions of the interlobular veins and their tributaries, and that the closely approximated lymphatic and venous channels may form a regulatory system for fluid exchange.

Pure Granulomatous Nocardiosis: A New Fungous Disease.

JOHN T. CUTTINO AND ANNE M. MCCABE (*The American Journal of Pathology*, January, 1949) describe a new disease entity in man characterized clinically by an abdominal mass, malnutrition, and an afebrile course. The morphological, cultural and biochemical characteristics of the causative organism, when contrasted with those of other organisms, present significant differences in every instance, justifying the designation of this organism as a new species to which the name "*Nocardia intracellularis*, n. sp." has been given. This organism is assigned to the genus *Nocardia*, family Actinomycetaceæ. In man the disease produced by this organism is a pure form of granulomatous inflammation characterized by phagocytosis of the pathogen by reticulo-endothelial cells and proliferation of these cells. In the spleen and lymph nodes the proliferation of macrophages is of such proportion as to displace completely the normal structure. There is equilibrium between the organism and its host cell to the extent that massive intracellular parasitism constitutes perhaps the most distinctive feature of the disease. Comparatively little necrosis occurs, and there is no response on the part of polymorphonuclear leucocytes and other inflammatory elements customarily found in the common infectious granulomata. *Nocardia intracellularis*, n. sp., produces a non-lethal disease in guinea-pigs, rats and mice. It produces no lesions in chickens, rabbits, frogs and goldfish. In the experimental animal, *Nocardia intracellularis*, n. sp., provokes a response which differs sharply from the reaction in man. This difference is to be found in comparatively extensive necrosis and relative paucity of intracellular organisms. The lesions heal rapidly in the experimental animal and are accompanied by the production of sensitivity of the tuberculin type.

Intracranial Vascular Lesions in Late Rheumatic Heart Disease.

JOHN DENST AND KARL T. NEUBUERGER (*Archives of Pathology*, September, 1948) state that lesions of intracranial vessels occur with unexpected frequency in late stages of rheumatic heart disease. The larger and smaller arteries and veins, mainly in the leptomeninges, show a great variety of pathological features. The principal lesions are various forms of thrombosis, endarteritic proliferation, alteration of the elastic membranes, and fibrosis of media and adventitia. The histological picture, as a rule, is sufficiently characteristic to permit differentiation from other vascular diseases that occur in the same location. Parenchymal changes in the brain secondary to the vascular processes are identical with those produced by other vascular diseases. Focal neurological signs may occur, but there is little evidence to show that the lesions described form the anatomical basis for psychotic syndromes.

Carcinoid Tumours of the Intestine.

ORVILLE F. GRIMES AND H. GLENN BELL (*Surgery, Gynecology and Obstetrics*, March, 1949) state that, in addition to the ordinary adenocarcinomata, superficially related tumours known as carcinoid or argentaffin tumours also appear in the gastro-intestinal tract. They occur as single nodules in the appendix, but are more often multiple elsewhere in the gastro-intestinal tract. In the appendix they appear in young people, contrasting markedly with their appearance elsewhere in patients whose average age is fifty-eight years. This report concerns eleven such tumours arising in the appendix and eight whose origins were in the small intestine. Those appearing in the appendix occurred as submucosal nodules extending peripherally to involve in succession the muscularis, the serosa, and in one instance the mesoappendix. All were treated by simple appendicectomy, after which no sequelæ were noted. At the opposite extreme are the eight patients exhibiting small bowel argentaffin tumours, all of which manifested malignant characteristics as shown by local or distant metastatic spread. The similarity of histological pattern and growth tendency leads one to believe that the tumours in either location are similar if not identical and that metastases and therefore apparent malignancy are merely a matter of time. In a small, narrow, blind-ending tube, such as the appendix, attention is called to the organ early,

so that the tumour is still a localized one when removed by simple appendicectomy. In the small bowel such early signs as are present are most often confused with abdominal conditions not requiring immediate surgical intervention. Hence intestinal tumours are not reached at such an early stage as are those in the appendix, so that metastases have had time to develop. Carcinoid tumours of the small bowel are most often seen in the terminal part of the ileum. Their predominant spread is regional, but widespread abdominal or distant metastases may occur, just as in the more common adenocarcinomata. Attention is called to the four most common symptoms and signs noted in carcinoid tumours of the small bowel. The tetrad of intermittent episodes of small-bowel obstruction associated with abdominal pain, diarrhœa and weight loss is so common, and indeed so characteristic, that consideration of such tumours is strongly advised when this syndrome appears. The radiological study of the small intestine in an attempt to demonstrate both kinking and tumour of the bowel is an important aid in obtaining a correct and early pre-operative diagnosis. The excellent results obtained from wide excision of the tumour-bearing area cannot be too strongly emphasized. Even when distant metastases have already occurred, it is not unusual to note a tendency toward stabilization of the metastatic deposits after the primary lesion has been removed. Post-operative irradiation may be beneficial, for there is suggestive though incomplete evidence that carcinoid tumours may be radiosensitive. It is because of these therapeutic tangibles that one should be especially alert to the possibility of the presence of carcinoid tumours. With early diagnosis and adequate resection one can expect better results in the surgical treatment of these tumours than in any other intestinal malignant tumour.

MORPHOLOGY.

Preaortic Hemiazygos Veins.

W. R. M. MORTON (*The Anatomical Record*, June, 1948) reports two cases in which the main drainage of the hemiazygos veins passed in front of the aorta and behind the œsophagus. The possible mode of development of the large pre-aortic venous anastomoses is considered and the dangers to the thoracic surgeon are indicated.

Innervation of Human Teeth.

S. BERNICK (*The Anatomical Record*, May, 1948) submits further evidence of the termination and looping of nerve fibres in the predentine and dentine.

Innervation of the Hip Joint.

E. GARDNER (*The Anatomical Record*, July, 1948) has studied the nerve supply of the human hip joint in dissections of adult joints and in serial sections of fœtal joints. The articular nerves arise from the femoral, obturator and superior gluteal nerves, from the nerve to the *quadratus femoris*, from the accessory obturator nerve when present, and possibly from branches of lumbar sympathetic ganglia. The branch or branches of the femoral nerve arise either directly from the femoral nerve or from its muscular branches. Most of them supply the ilio-femoral ligament, especially near its femoral attachment, and the neighbouring portion of the femur. A branch of the nerve to the pectineus supplies the antero-medial region of the capsule and the neighbouring portion of the femur, and overlaps the area reached by the obturator nerve. The articular branch of the obturator nerve supplies the medial portion of the capsule (pubo-capsular ligament), where it ramifies in the fibrous layer of the capsule. Some fibres reach the synovial tissue and also course along the *ligamentum teres* to the femur. When the accessory obturator nerve is present it supplies the area usually reached by the branch of the femoral nerve to the pectineus muscle. The nerve to the *quadratus femoris* muscle gives one or two fine twigs which enter the ischio-capsular ligament near its femoral attachment. The superior gluteal nerve gives rise to twigs, which course in the fibrous layer of the supero-lateral region of the capsule and reach anteriorly and inferiorly toward the area supplied by the femoral nerve. It is possible that sympathetic fibres from lumbar ganglia reach the joint by following articular vessels. It is probable that many of the nerve fibres supply blood vessels in the capsule and neighbouring bone. Little can be said about other types of endings except that the concentration of fibres in the antero-medial region of the capsule makes it seem likely that proprioceptive endings are located here.

Congenital Absence of the Tibia.

J. E. GRAY (*The Anatomical Record*, June, 1948) states that although some 120 cases of congenital absence of the tibia have been reported, the appearances on dissection of the abnormal limb have rarely been described. He describes the amputated leg of a boy of three years, in which there was congenital absence of the tibia, talus, navicular, cuneiforms, two metatarsals and the three medial toes. The *tibialis posterior, extensor hallucis longus, extensor digitorum brevis, abductor hallucis, flexor hallucis brevis*, first and second lumbricals, transverse head of the *adductor hallucis* and medial interosseous muscles were also absent. A large supernumerary muscle "peroneo-tarsus" was present. Other muscles had abnormal insertions. The muscular abnormalities were not connected with the segmental nerve supply. It is suggested that the defect extended to include the corium of the medial side of the sole. The great saphenous vein, the saphenous nerve and muscular branches of the medial plantar nerve were also absent. The literature is reviewed. A critical survey of possible causes of the defect is made.

Human Foramen of Magendie.

M. L. BARR (*Brain*, September, 1948) records observations on the variations in size and configuration of the foramen of Magendie (median aperture of the fourth ventricle) in a series of 118 adult human brains removed at autopsy. He states that in 89% of the specimens examined, the foramen is of variable but considerable size, with an average size of sixteen square millimetres. In 7% of the specimens the membranous roof of the fourth ventricle is more intact than usual, but the foramen is still seven square millimetres in size on the average. In 3% of this series the roof is almost complete, the foramen being represented by a minute aperture a millimetre in diameter or less. Finally, in a single brain a foramen of Magendie is lacking. The possible implications of these observations in encephalography are discussed.

Anatomy of Cerebral Circulation.

H. A. SHANKIN *et alii* (*Archives of Neurology and Psychiatry*, September, 1948) give an account of cerebral studies performed on living man to determine not only anatomical pathways but also the dynamic circulatory patterns. By means of dye-injection technique in living human subjects, the partition and distribution of the circulation of the head were studied. Evidence is presented that blood entering the brain via each internal carotid artery is distributed almost wholly to the ipsilateral hemisphere and drained predominantly by the internal jugular vein on the corresponding side. Evidence is presented that blood in each internal jugular vein is fairly representative of the drainage from all the histological components of the brain. The data indicate that blood in the internal jugular vein at the level of the superior bulb is relatively free of blood derived from extracerebral sources. On the other hand, blood in the external jugular vein contains a significant fraction of cerebral venous blood. In seven patients the total cerebral blood flow was estimated by a dye-dilution technique from samples obtained simultaneously from the internal jugular bulbs. The relation of these findings to various suggested methods for measuring human cerebral blood flow is discussed.

True Hermaphrodism in Adult Human.

W. H. G. PATTON (*The Anatomical Record*, August, 1948) records a case of true hermaphrodism in the human. Up to the present time probably not more than twenty cases have been described. The present case is that of a patient, who, although masquerading as a male and performing manual labour, was considered to be mainly a female. However, on examination both male and female sex organs were found. Histological examination proved that the female gonad was functioning. This was also borne out by the fact that the patient menstruated regularly and exhibited other secondary female characteristics.

Human Pulmonary Vein.

J. AUËR (*The Anatomical Record*, August, 1948) discusses the views put forward concerning the development of the pulmonary vein. It is believed to be either an outgrowth of the sino-atrial region of the heart or a differentiation of the splanchnic plexus of veins formed around the primitive gut. The author describes in a series of human embryos, caudal and cranial evaginations of the sino-atrial region into the dorsal mesocardium. The cranial type is usually a single outpocketing giving rise to the stem of the pulmonary vein, which later makes contact with the capillaries of the splanchnic plexus. The caudal type may be paired (as in the rat) and normally disappears with the extensive changes seen in the *sinus venosus*. Persistence of the caudal evagination may lead to anomalous pulmonary veins emptying in either the *sinus coronarius, vena cava inferior, vena cava superior* or right atrium.

British Commonwealth Medical Conference.

SASKATOON MEETING.

THE first annual British Commonwealth Medical Conference was held at Saskatoon, Saskatchewan, Canada, on June 7, 8 and 9, 1949.

The delegates attending the meeting were as follows:

Australia: Dr. J. G. Hunter, General Secretary of the Federal Council of the British Medical Association in Australia.

Canada: Dr. William Magner, President of the Canadian Medical Association, Saint Michael's Hospital, Toronto, Ontario; Dr. Harris McPhedran, Chairman of the General Council of the Canadian Medical Association, Medical Arts Building, Toronto 5, Ontario.

Ceylon: Dr. C. C. de Silva, President of the British Medical Association (Ceylon Branch), Maradand, Colombo.

Eire: Dr. P. J. Delaney, Secretary of the Medical Association of Eire, 95 Merrion Square, Dublin.

Great Britain: Dr. H. Guy Dain, Chairman of the Council of the British Medical Association, Tavistock Square, London, W.C.1; Dr. Charles Hill, Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

India: Dr. S. C. Sen, Honorary Secretary, Indian Medical Association, 1 Barakhamba Road, New Delhi.

Newfoundland: Dr. Howard Drover, Bay Robert, Newfoundland.

New Zealand: Dr. J. O. Mercer, Chairman of the Council of the British Medical Association, New Zealand Branch, Wellington.

Pakistan: Dr. N. Ahmed, President of the Pakistan Medical Association, Chittagong, East Pakistan.

South Africa: Dr. A. H. Tonkin, Medical Secretary of the Medical Association of South Africa, 35 Wale Street, Capetown.

Southern Rhodesia: Dr. C. S. Dismorr, Honorary Secretary of the Mashonaland Branch of the British Medical Association, Box 170, Salisbury.

The chair was occupied by Dr. J. F. C. Anderson, President-Elect of the Canadian Medical Association, who had been elected president at the inaugural meeting held in London on September 15 and 16, 1948; Dr. T. C. Routley, General Secretary of the Canadian Medical Association, was the Secretary of the Conference.

In declaring the Conference open, Dr. J. F. C. Anderson extended a warm welcome to the delegates. Dr. H. Guy Dain replied on behalf of the delegates.

The Conference then proceeded to consider the recommendations made by the inaugural meeting, which had been submitted to the various medical associations for their approval, particularly those dealing with (*a*) the desirability of developing closer personal and professional relations through their national medical associations or units between the nations linked in the Commonwealth, and (*b*) the frequency with which such conferences should be held. In regard to (*a*), there were no dissentient voices, the unanimous opinion being that the holding of such conferences would be of inestimable value. In regard to (*b*), there was considerable discussion. Whilst the unanimous opinion was that it was desirable that the Conference should be held annually, it was felt that the cost of sending delegates to yearly conferences would prove difficult for most of the associations. It was agreed that the frequency of conferences would depend in some measure on the results obtained.

The general feeling was that for the present the Conference should be held yearly, and the next conference will be held in Brisbane, Australia, in May, 1950.

In regard to officers, it was decided:

(i) That the president be chosen by the member association in whose area the Conference will be held.

(ii) That an honorary secretary and treasurer be appointed, whose duties will be to carry out the instructions of the Conference, and in consultation with the president and local secretary prepare the draft agenda. (It was decided that the British Medical Association be invited to allow its secretary to act as honorary secretary-treasurer.)

(iii) That there shall be a local secretary, who shall be the secretary of the member association in whose area the conference will be held, and whose duties will be to prepare the draft minutes, and make all the necessary arrangements for the Conference.

The general part of the business occupied Tuesday morning and Thursday afternoon. On Tuesday afternoon and Wednesday and Thursday mornings, papers were presented as follows:

Tuesday afternoon: Dr. Gordon Ferguson, Saskatoon (Secretary of the Saskatchewan Division of the Canadian Medical Association, and Registrar of the College of Physicians and Surgeons of Saskatchewan[1]), "Medical Licensure in Canada"; Dr. A. L. Caldwell, Saskatoon, "Prepaid Medical Care Plans in Canada"; Dr. George Ferguson, Fort San, "The Provision of Tuberculosis Prevention and Care in Canada".

Wednesday morning: Dr. Harvey Agnew, Toronto, Secretary of the Canadian Hospital Council, "Hospitalization Services in Canada"; Dr. J. Lloyd Brown, Regina, Saskatchewan, "The Swift Current Health Insurance Scheme"; Dr. W. P. Warner, Ottawa, Director-General of Treatment Services, Department of Veterans Affairs (corresponding to the Department of Repatriation in Australia), "Medical Care of Veterans in Canada".

Wednesday afternoon: Dr. G. D.-W. Cameron, Ottawa, Deputy Minister, Department of National Health and Welfare, "Canada's Federal Health Programme"; Dr. William Magner, Toronto, "The Organization and Management of a National Medical Association"; Dr. Victor Johnston, Lucknow, "Federal and Provincial Health Legislation in Canada".

Thursday morning: Dr. John W. Scott, Dean of the Faculty of Medicine of the University of Alberta, "Undergraduate Medical Education in Canada"; Dr. D. Sclater Lewis, Montreal, "Post-Graduate Medical Education in Canada"; Dr. Harris McPhedran, Toronto, "The Future of Medicine in Canada".

It will be seen that the papers covered a wide range of subjects and provided useful information about conditions of medical practice and the trend of medical thought in Canada. The Conference agreed that constituent medical associations should be permitted to publish the papers for the information of their members.

Questions were asked of the readers of the papers, and members of the other medical associations were in some cases able to give a short account of what was happening in their respective countries.

On the question of reciprocity the Conference adopted the following resolution:

> That this Conference welcomes the moves towards wider reciprocity for medical registration in the countries of the Commonwealth and suggests consideration for wider facilities for reciprocity be considered.

The Conference met in the Board room of the University of Saskatchewan on Tuesday, June 7, and Wednesday, June 8, 1949, and at the Bessborough Hotel on Thursday, June 9. The value of the personal contact in conferences such as this is inestimable, and the delegates attending the Conference were able to obtain information about what was happening in the various countries of the Commonwealth which it would not have been possible to obtain in any other way. To Dr. J. F. C. Anderson (President-Elect of the Canadian Medical Association) and Mrs. Anderson, and to the Executive, officers and members of the Canadian Medical Association, the delegates attending the Conference were under a deep debt of gratitude for their more than generous hospitality.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held at the Royal Prince Alfred Hospital on May 19, 1949. The meeting took the form of a series of clinical demonstrations by members of the honorary medical and surgical staff of the hospital. Part of this report appeared in the issue of June 25, 1949.

Carcinoma of the Cervical Part of the Œsophagus.

DR. N. R. WYNDHAM presented a female patient, aged thirty-eight years, who had been treated for pernicious anæmia, during the course of which she developed a carcinoma just below the level of the cricoid cartilage. After biopsy, the growth and adjacent parts of the gullet

[1] This body corresponds to the Medical Boards in Australia—that is, it is a licensing body, but is not a scientific body. In Saskatchewan the Division of the Canadian Medical Association and the College of Physicians and Surgeons are one and the same body.

and pharynx were removed and a skin tube, fashioned from the neck, was made to repair the defect. The operation had been performed eighteen months before the meeting.

Carcinoma of the Recto-Sigmoid Junction.

Dr. Wyndham then showed three patients who had undergone operation for carcinoma of the recto-sigmoid junction up to two and a half years previously. The anal canal and last one and a half inches of the rectum had been preserved and the continuity of the bowel reconstituted by an anastomosis through the floor of the pouch of Douglas. No functional difficulty was present.

Transthoracic Total Gastrectomy.

DR. E. V. BARLING presented a patient, aged sixty-two years, who had been sent into hospital with a diagnosis of carcinoma of the stomach regarded as inoperable, mainly because of the frank palpability of the tumour. At operation the tumour was found to be of a fungating type, filling most of the gastric lumen; there was evidence of only local spread into the transverse mesocolon. Use of the transthoracic approach made the condition readily operable. Dr. Barling said that the patient had gained some five pounds in weight in the past week, in spite of the usual upset experienced by such patients with feeding direct into the jejunum. The patient was shown to illustrate, firstly, that operability could be finally determined only at laparotomy, in the absence of evidence of embolic forms of metastasis, and secondly, that the upset in digestion occasioned by œsophago-jejunostomy with enteroanastomosis could be overcome and the patient could put on condition. It was too early, of course, to be optimistic about the ultimate outcome for the patient under discussion.

Duodenal Diverticulum.

Dr. Barling next presented a patient, aged fifty-eight years, who had had persistent indigestion for two years, with bouts of vomiting occurring more frequently in the latter part of that period; the patient felt that the outlet to his stomach was blocked. X-ray examination carried out twice at two of the large hospitals had revealed no abnormality. Clinically the patient had evidence of gastric retention, and further X-ray examination revealed both a posterior duodenal ulcer and a large diverticulum of the third part of the duodenum, which filled up rapidly on the ingestion of a barium meal, and caused delay in pyloric emptying, as it passed up in relation to the first inch of the duodenum. There was much tenderness over the diverticulum, and it was considered that it rather than the small duodenal ulcer was the cause of the patient's illness. It was intended to treat the patient conservatively for a start, and to resort to surgery only if the conservative régime failed. The patient was shown to draw attention to the increasingly frequent recognition of the fact that duodenal diverticula did cause symptoms that required surgical intervention, and also to the fact that X-ray examination of the stomach needed to be painstakingly carried out.

Low-Thigh Amputation for Arteriosclerosis.

Dr. Barling's third patient was a man, aged sixty-nine years, who had had thrombosis of the femoral vessels of the right leg below the origin of the *profunda femoris* branch. He had generalized arteriosclerotic changes, and was in a preuræmic state when first examined by Dr. Barling; gangrene of the leg was present at that time to a level just below the knee. It was decided to attempt a low-thigh amputation after the method of Callender, as experience had shown that amputation through the classical site in the thigh was not productive of good healing, and that failure to obtain good healing usually meant a prolonged stay in bed with consequent bed sores and ultimately death. The operation had been carried out, and the patient was shown with a soundly healed stump fourteen days after the operation. His renal function was much improved, and he was mobile on his crutches. It was thought that the technique was a distinct advance on the old method, mainly owing to the bloodless field and the lack of hæmatoma occurring in the wound as a complication.

Femoral Hernia following Inguinal Repair.

A male patient, aged thirty-nine years, was shown, who had undergone right inguinal herniorrhaphy some two years previously, and had been admitted to hospital with a strangulated femoral hernia on the same side. He was shown to emphasize the fact that what was in effect a form of recurrence had followed inguinal herniorrhaphy, and also to provoke discussion on the merits of the operation recently publicized by McVay and Anson. In that operation an attempt was made to prevent the leaving of weakness at the internal ring in the posterior wall of the canal or at the site of the femoral canal by standardization of the procedure to be adopted in the repair of the three main forms of hernia in the region—namely, indirect inguinal, direct inguinal and femoral.

Post-Traumatic Rupture of the Stomach.

Dr. Barling's next patient had had an accident while riding on a motor-cycle after a "feed" of fruit salad. He was found to have rigidity of the upper part of the left side of the abdomen, with audible bowel sounds. He was suffering from shock, and rupture of the spleen was suspected. At laparotomy the peritoneal cavity was found to contain blood mixed up with undigested fruit salad. The stomach was ruptured on its anterior surface, the tear extending onto the greater curvature in the region of the *vasa brevia*, which were torn through in the lower part of the gastro-splenic ligament. The patient had an associated comminuted fracture of the left humerus, but made an uneventful recovery after repair of the gastric rent, ligation of the torn vessels and setting of the fractured humerus.

Severed Flexor Tendon of the Finger.

Dr. Barling then presented a man, aged thirty-three years, who had had a stamping-machine injury to the middle finger of the left hand, causing a laceration of the soft tissues on the flexor aspect of the proximal phalanx of the finger. Flexion of the finger was not possible prior to operation, at which it was found that the *flexor digitorum sublimis* tendon had been severed in the flexor tunnel, and the swollen contracted ends of the tendon were blocking the tunnel. The ends of the tendon were excised as far proximally and distally as possible, the sheath was repaired and the skin was sutured. Movements were instituted immediately, and the patient was shown to have a 90% functional result already at a period fourteen days after operation.

Compound Fractures.

Finally Dr. Barling showed a series of patients, who had sustained compound fractures of the lower limbs, in many cases multiple fractures of both lower limbs. The patients were shown to emphasize the change brought about by the availability of penicillin in the treatment of compound fractures, in that anatomical results could be obtained in a much shorter time, and that multiple fractures were much less worrying for those treating them when they could be fixed anatomically by a plate, without the necessity for very complicated traction arrangements. One patient particularly mentioned had had a fracture of the left tibia, the right femur and the lower part of the right radius, with dislocation of the right elbow joint and head injuries. Another patient in the group had recovered after fat embolism.

Tumour of the Clavicle.

DR. P. A. TOMLINSON presented a female patient, aged fifty-eight years, with a tumour of the medial end of the right clavicle. The patient had first consulted him because of dilated veins passing from the right arm to the chest wall. She made no comment about the tumour at the time. On examination of the patient, there was no dilatation of the right jugular venous system; but a tumour of the medial end of the clavicle was present, obstructing the right subclavian vein. X-ray examination revealed that the medial end of the clavicle was replaced by a tumour extending upwards into the root of the neck and backwards, displacing the apex of the pleura. The Wassermann reaction was present in the blood. Dr. Tomlinson said that the tumour had decreased in size and the patient had gained over one stone in weight since the institution of anti-specific treatment.

Air Pyelography.

Dr. Tomlinson then presented a small series of X-ray films showing the use of air pyelography. It was demonstrated that air provided a greater contrast than iodide in the localization of radio-opaque stones in the urinary tract. The diagnostic procedure was considered to be of special value in the interpretation of doubtful shadows lying over the transverse processes and lateral mass of the sacrum.

Frontal and Ethmoidal Sinusitis with Complications.

DR. E. MCA. STEEL presented a boy, aged fifteen and a half years, who had been admitted to hospital on February 9, 1949, with a history of headache between the eyes for three

days and pain, swelling and tenderness of the forehead and eyelids present for one day. He had had "'flu" two weeks previously, and had been swimming three days before his admission to hospital. He had no history of any injury. On examination, the patient had much boggy swelling of the forehead, the bridge of the nose and both upper eyelids. There was a point of maximal tenderness at the left inner canthus. His temperature was 104·8° F. Examination of the nose, ears, throat and eyes revealed no definite abnormality. X-ray examination revealed dulness of both maxillary sinuses, greater on the right side than on the left, with slight haziness of the ethmoid and frontal sinuses. A blood count disclosed a moderate degree of leucocytosis with relative neutrophilia. Chemotherapy was commenced immediately, with intramuscular injections of penicillin, 100,000 units every three hours, and sulphadiazine, in an initial dose of three grammes and then one gramme every four hours. On the day after the patient's admission to hospital, the swelling of the frontal region and eyelids had increased, and on February 11 chemosis of the left eye had appeared, with proptosis and loss of vision. The eyelids were very œdematous, and a large, tender swelling, which appeared to be fluctuant, extended over the whole frontal region. Pus was present in the left middle meatus of the nose. Dr. N. McA. Gregg, who examined the patient in consultation, reported intense œdema of the eyelids of each eye. He was unable to obtain a view of the right eye, but stated that in the left eye movements were limited in all directions, the pupil was active, and although there was no swelling of the optic nerve head, the veins of the fundus were engorged and almost black in appearance. He made a provisional diagnosis of cavernous sinus thrombosis. At operation pus was obtained by aspiration of the frontal swelling. A central incision was made from below the hairline to the root of the nose, and a large subperiosteal collection of pus was evacuated. No sinus was found in the frontal bone. The incision was extended laterally on both sides from the root of the nose, and a bilateral obliterative frontal sinus operation was carried out. Both frontal sinuses were full of pus. The *lamina papyracea* was broken through on each side, and infected anterior ethmoidal cells were removed. No pus was found in the orbital cavities. The cavities were filled with penicillin-sulphanilamide powder and closed, except for a small tube at each inner canthus, which was removed after forty-eight hours. Lumbar puncture produced clear fluid under pressure of 200 millimetres of cerebro-spinal fluid. Intravenous saline therapy was commenced. Culture of pus from the subperiosteal abscess produced a growth of *Staphylococcus aureus*, which was coagulase-positive and sensitive to both penicillin and streptomycin. Chemotherapy was given, with penicillin, streptomycin and sulphadiazine, and in view of the possibility of cavernous sinus thrombosis, treatment with dicoumarol and heparin was first instituted; 300 milligrammes of dicoumarol were given on the first day, 200 milligrammes on the second day and 100 milligrammes on the third day, and 5000 units of heparin were given intravenously every four hours. On the day after operation a tender lump developed over the right lumbo-sacral joint, which was thought to be a secondary abscess, but it subsided without special treatment. Convalescence was otherwise uneventful, and the patient was discharged to the out-patient department on March 1, 1949.

Osteogenesis Imperfecta.

DR. L. J. WOODLAND and DR. W. D. STURROCK showed a male child, aged two years, who, following a normal birth, had had a fracture of the right femur and left tibia; since birth he had had in all about thirty fractures confined entirely to the long bones of the lower limbs. He displayed the usual features of *osteogenesis imperfecta*, namely, fragility of bone, osteomalacia, blue sclerotics, atonic muscles, lax joints and dwarfing. The milk teeth were waxy in appearance, but dentition was not delayed. X-ray pictures taken at birth showed that the long bones were shorter and broader than normal; the internal cancellous structure was deficient and a pencil-line cortex was seen. Recent X-ray films revealed narrow osteoporotic shafts of long bones, whilst the extremities of those bones showed club-like expansion; the ribs showed irregular bending and the skull deficient ossification. As was usual in cases of *osteogenesis imperfecta*, the child was normal mentally but retarded physically. As yet he has been unable to sit up. There was no familial history, which occurred in 50% of cases. It was pointed out that patients with the prenatal or the intrapartum types of *osteogenesis imperfecta* seldom lived long. X-ray films in the case under discussion showed the transition from the early broad-bone, ante-partum, severe type to the narrow-shaft, less severe type. It was pointed out that in the disease, whilst the blood chemistry was normal, the subperiosteal cells were deficient in phosphatase.

Congenital Abnormality of the Odontoid Process.

The second patient was a male child, aged ten years, who gave a history that early in January, 1946, a heavy child jumped on his back whilst he was swimming. He was forced under the water with his neck acutely flexed. When he climbed out of the baths he noticed a clicking noise on rotation of his neck. There was also noticed a slight ache about the level of his seventh cervical vertebra. After a few minutes he jumped off the diving board feet first into the water. After this he had difficulty in keeping his head above water. When he climbed out of the water, his mother noticed the clicking noise on rotation of his head. There was no history of any previous injury. X-ray examination in the country revealed slight anterior subluxation of the atlas on the axis. A plaster cast was applied and he was transported to Sydney. Dr. Woodland said that he had first examined the child on January 15, 1946, when after the cast was removed an X-ray examination showed a moderate posterior subluxation of the atlas on the axis. An antero-posterior view revealed a very shallow odontoid process with widening of the joint space between the articular facets of the interarticular joints between the first and second cervical vertebræ and slight asymmetry of the articular surfaces. The child had no symptoms. On examination, the alignment of his head and neck appeared to be normal. There was no muscle spasm. He complained of slight tenderness on pressure over the spinous process of the seventh cervical vertebra and also over the second cervical vertebra. Movement of his head was possible through a normal range. At the extreme of all movements he complained of slight generalized aching over the posterior aspect of the neck. He was later conveyed to the X-ray department, where a lateral X-ray picture, taken with the neck in neutral position, showed a normal relationship of the atlas and axis. Another film was taken after the head and neck had been carefully flexed. That film showed that the atlas had moved forward about one-half the width of the odontoid process. A film taken with the head extended showed that the tip of the odontoid process articulated with the inferior surface of the anterior arch of the atlas. The child was placed in a plaster cast of Minerva type until March 4, 1946, when further X-ray films showed that there was still undue mobility between the atlas and axis. In view of the absence of clinical signs or symptoms plaster fixation was not persisted in. The child had worn a leather collar for a few months, and subsequently had led a normal life without symptoms. It was pointed out that the difficulty in treating the patient was to assess how much of the undue mobility was due to congenital anomaly and how much to recent injury. The fact that there was slight asymmetry of the articular facets with the atlas tilted slightly to the left suggested that recent injury was a material factor, even though the symptoms were minimal. The development and ossification of the axis were rather complicated and various congenital abnormalities might be expected. Instability of the atlas on the axis was likely when the odontoid process was underdeveloped or absent. Four cases of congenital absence of the odontoid process had been reported in the literature; three of the patients came under observation because of recent injury, the other because of old injury with persistent symptoms.

Ununited Fracture of the Odontoid Process.

The third patient of the group presented by Dr. Woodland and Dr. Sturrock was a male, aged thirty-one years, who gave a history that on January 10, 1949, he suddenly flexed his head to avoid hot steel and felt a sharp pain behind his neck. The pain was relieved by heat therapy. An X-ray picture taken by his private practitioner on February 9, 1949, showed a fracture through the base of the odontoid process with slight separation of the fragments. The patient was placed in a Minerva jacket for three months. On removal of the jacket X-ray examination showed non-union of the odontoid process and slight subluxation of the first cervical vertebra on the second. At the time of the meeting the patient had no symptoms and was wearing a Thomas collar. It was proposed to effect fusion between the spinous processes of the first and second cervical vertebræ, but so far the patient had not consented to operation. It was pointed out that this patient and the previous patient illustrated the fact that when the odontoid process was abnormally short or, as in the case under discussion, the site of an ununited fracture through the base, undue mobility occurred between the first and second cervical vertebræ. Apparently the ligaments of the interarticular joints between the pedicles were alone not sufficiently strong to prevent subluxation. The normal odontoid process and the very strong and extensive ligamentous structures radiating from the odontoid to the occiput

and the upper two cervical vertebræ were necessary for complete stability.

Intramedullary Nail Femur.

The fourth patient was a male, aged twenty-eight years, who had incurred a compound fracture of the left femur on January 25, 1947. He was treated in a country hospital by weight traction for six weeks and then application of a plaster cast. Subsequently he was treated in a Thomas bed knee splint. He was admitted to Royal Prince Alfred Hospital in June, 1947, and on July 9, 1947, an onlay graft, taken from the tibia, was screwed onto the femur. Union appeared to be occurring and he was allowed up in a walking caliper on December 1, 1947. The graft fractured. Further immobilization and the additional insertion of bone chips did not produce union. On September 14, 1948, a Kuntzer nail was inserted after the fracture site had been freshened. On November 3, 1948, he commenced walking in a caliper, but taking weight on the heel. On February 21, 1949, the caliper was discarded, reasonably firm bony union being present. It was pointed out that the indications for the use of a Kuntzer nail in the treatment of fracture of the femur were limited. The fracture must be in the proximal half of the femur and the use of the nail was not advocated until conservative treatment had failed.

Ewing's Tumour.

The last patient in the group was a boy, aged six years, who had been admitted to hospital six months before complaining of acute pain in the right hip. He had a high temperature and a leucocyte count of 15,000 per cubic millimetre. Radiographs revealed a rarefied area of the upper end of the left femur with some periosteal new-bone formation. Three weeks later, at operation, grey semisolid material was curetted from the cavity, and the cavity partially filled with a tibial graft. Histologically the biopsy material resembled granulation tissue, but with a considerable number of large mononuclear cells; a diagnosis of Ewing's tumour was considered unlikely. Five months later the patient was readmitted to hospital with a rapidly growing swelling now three inches in diameter in the mid-frontal region. Further radiographs revealed a defect in the frontal bones, but in the femur, although the original cavity could still be seen, the tibial graft was firmly incorporated. A course of deep X-ray therapy caused the rapid disappearance of the frontal tumour.

(To be continued.)

Correspondence.

FEDERAL MEDICAL WAR RELIEF FUND.

SIR: The announcement in the monthly circular of the New South Wales Branch of the British Medical Association that the Federal Council has decided to close this fund at the end of this month prompts me to remind all medical men as well as the families of deceased medical men who served overseas in the Great Wars that very valuable guidance and assistance is offered by Legacy in the problems of education and employment.

Should there be any among the forty young people mentioned in the circular who are not known to Legacy, news of them would be appreciated, and they may be assured that, however and whenever possible, Legacy throughout Australia will do everything possible to help them.

Yours, etc.,

ERIC P. BLASHKI,
Vice-President, Sydney Legacy.

193 Macquarie Street,
Sydney,
June 20, 1949.

CONTINUOUS POSTURAL DRAINAGE.

SIR: Could you be so kind as to allow me to make the following corrections in your reproduction of my paper on continuous postural drainage in your issue of June 18, 1949.

In Figure II the diagram of either lung should be inverted in order to appreciate the relative value of the prone or

DISEASES NOTIFIABLE IN EACH STATE AND TERRITORY OF AUSTRALIA AND NOTIFICATIONS FOR THE WEEK ENDED JUNE 11, 1949.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[3]
Anchylostomiasis	*	..	..	..	*	..	..	..	..
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	1	1	..	..	1	2	..	..	5
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	4	..	..	..	..	..	4
Diphtheria	8	9	3	..	..	..	..	..	20
Dysentery(*b*)	*	..	..	..	..	..	..	..	..
Encephalitis Lethargica	..	1	..	..	..	..	..	..	1
Erysipelas	*	*	*	..	*	*	..	..	..
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	1	*	*	*	*	*	..	1
Influenza	*	*	*	..	..	*	..	*	..
Leprosy	..	..	..	..	..	..	..	..	..
Malaria(*c*)	*	(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	(*c*)
Measles	*	*	*	62	*	*	..	..	62
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	3	8	..	..	3	..	..	..	14
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	2	1	..	1	..	..	..	..	4
Rubella	*	*	*	*	*	*	..	1	1
Scarlet Fever	26	27	6	10	4	..	..	1	74
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	..	2	*	*	*	*	*	2
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	51	17	10	5	3	5	..	..	91
Typhoid Fever(*e*)	..	..	..	1	1	..	..	..	2
Typhus (Endemic)(*f*)	2	..	..	..	..	..	..	..	2
Undulant Fever	..	..	1	..	..	..	..	..	1
Weil's Disease(*g*)	*	*	..	*	*	*	*	*	..
Whooping Cough	*	*	*	34	*	*	..	..	34
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 36, 1944-1945.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from Northern Territory
* Not notifiable.

(*a*) Includes "Mossman" and "Sarina" fevers. (*b*) Includes amœbic and bacillary. (*c*) Statistics inexact with varying practice with regard to relapses in Service cases infected overseas. (*d*) Includes all forms except in New South Wales and Northern Territory, where only pulmonary tuberculosis is notifiable. (*e*) Includes enteric fever and paratyphoid fevers. (*f*) Cases reported are all of the mild type known as Brill's disease or endemic typhus (including scrub and urban types). (*g*) Includes leptospiroses, Weil's and Para-Weil's disease.

semi-prone position in segmental drainage, the posterior basic segments being those most commonly affected.

In the first paragraph of conclusions, line 4, please remove the "are" following "acute exacerbations" and insert after the comma following "intercurrent infections" in line 5.

Thanking you in anticipation.

Yours, etc.,
L. BEDFORD ELWELL.

Ballow Chambers,
Wickham Terrace,
Brisbane.
June 22, 1949.

NATIONAL HEALTH SERVICE.

SIR: From time to time reference has been made to the stated objective of the Federal Government ultimately to replace private medical practice with a Government service. The following statement of the Attorney-General, Dr. H. V. Evatt, throws some light on what might be Government policy on the right of any person to undertake the study of medicine as a preliminary to practice. This statement was reported as being made at the summer school of the Australian Institute of Political Science in 1944. It was repeated in Parliament in the presence of the Attorney-General, and he did not deny its correctness.

> The taking away of the right of the individual to choose his own vocation and employer was only one of the freedoms which the Australian people must forgo in the interests of the State.
> . . . . Today, with the enormous development of industry and industrial organization, corporate control and finance, there is no longer a full right in every person to choose his own vocation in life.

Members are invited by the Federal Publicity Committee to quote this statement as an indication of the lengths to which a very senior Minister is prepared to go in the curtailment of simple freedoms.

Yours, etc.,
J. H. PRIESTLEY,
Assistant General Secretary, Federal Council of the British Medical Association in Australia.

British Medical Association House,
135 Macquarie Street,
Sydney.
June 23, 1949.

Obituary.

FREDERICK JOHN JUDE.

WE regret to announce the death of Dr. Frederick John Jude, which occurred on May 30, 1949, at Adelaide.

WILLIAM HENRY ORCHARD.

WE regret to announce the death of Dr. William Henry Orchard, which occurred on June 20, 1949, at Malvern, Victoria.

Medical Appointments.

Dr. C. Y. Bland has been appointed Deputy Medical Superintendent, Department of Public Health, New South Wales.

Dr. P. A. Green has been appointed as Deputy Quarantine Officer at Port Kembla, New South Wales, under the *Quarantine Act*, 1908-1947.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Hewer, George Frederick, M.B., Ch.M., 1919 (Univ. Sydney), Narromine, New South Wales.

St. Vincent Welch, John Basil, M.B., B.S., 1948 (Univ. Sydney), Number 2 Flat, 14 Murdoch Street, Cremorne.

Howell, William Hessel, M.B., B.S., 1948 (Univ. Sydney), Marrickville District Hospital, Marrickville.

Diary for the Month.

JULY 5.—New South Wales Branch, B.M.A.: Council Quarterly Meeting.
JULY 6.—Victorian Branch, B.M.A.: Branch Meeting.
JULY 6.—Western Australian Branch, B.M.A.: Council Meeting.
JULY 7.—South Australian Branch, B.M.A.: Council Meeting.
JULY 8.—Queensland Branch, B.M.A.: Council Meeting.
JULY 12.—New South Wales Branch, B.M.A.: Executive and Finance Committee. Organization and Science Committee.
JULY 14.—Victorian Branch, B.M.A.: Organization Subcommittee.
JULY 18.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135 Macquarie Street, Sydney): Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester United Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

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